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L14: Entry 17 of 55

File: USPT

Jan 23, 2001

US-PAT-NO: 6177272

DOCUMENT-IDENTIFIER: US 6177272 B1

TITLE: Method for treating vascular proliferative diseases with p27 and fusions thereof

DATE-ISSUED: January 23, 2001

## INVENTOR-INFORMATION:

| NAME                | CITY      | STATE | ZIP CODE | COUNTRY |
|---------------------|-----------|-------|----------|---------|
| Nabel; Gary J.      | Ann Arbor | MI    |          |         |
| Nabel; Elizabeth G. | Ann Arbor | MI    |          |         |

## ASSIGNEE-INFORMATION:

| NAME                                      | CITY      | STATE | ZIP CODE | COUNTRY | TYPE CODE |
|---|-----------|-------|----------|---------|-----------|
| The Regents of the University of Michigan | Ann Arbor | MI    |          |         | 02        |

APPL-NO: 8/ 897333 [PALM]

DATE FILED: July 21, 1997

INT-CL: [7] C12 N 15/63, C12 N 15/85, A61 K 48/00, C07 H 21/04

US-CL-ISSUED: 435/320.1; 435/455, 530/350, 536/23.1, 536/23.4, 536/23.5, 536/24.1

US-CL-CURRENT: 435/320.1; 435/455, 530/350, 536/23.1, 536/23.4, 536/23.5, 536/24.1

FIELD-OF-SEARCH: 435/320.1, 435/455, 514/44, 536/23.1, 536/23.4, 536/23.5, 536/24.1, 530/350

## PRIOR-ART-DISCLOSED:

## U.S. PATENT DOCUMENTS

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| PAT-NO  | ISSUE-DATE     | PATENTEE-NAME | US-CL     |
|---------|----------------|---------------|-----------|
| 5672508 | September 1997 | Gyuris et al. | 435/320.1 |
| 5863904 | January 1999   | Nabel et al.  | 514/44    |

## FOREIGN PATENT DOCUMENTS

| FOREIGN-PAT-NO | PUBN-DATE     | COUNTRY | US-CL     |
|----------------|---------------|---------|-----------|
| WO 95/18824    | July 1995     | WOX     | 514/44    |
| WO 9602140A1   | February 1996 | WOX     | 435/320.1 |
| WO 96/25507    | August 1996   | WOX     |           |

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L14: Entry 22 of 55

File: USPT

May 30, 2000

US-PAT-NO: 6068982

DOCUMENT-IDENTIFIER: US 6068982 A

TITLE: Ubiquitin conjugating enzymes

DATE-ISSUED: May 30, 2000

## INVENTOR-INFORMATION:

| NAME                | CITY               | STATE | ZIP CODE | COUNTRY |
|---------------------|--------------------|-------|----------|---------|
| Rolfe; Mark         | Newton Upper Falls | MA    |          |         |
| Chiu; Maria Isabel  | Boston             | MA    |          |         |
| Cottarel; Guillaume | West Roxbury       | MA    |          |         |
| Berlin; Vivian      | Dunstable          | MA    |          |         |
| Damagnez; Veronique | Cambridge          | MA    |          |         |
| Draetta; Giulio     | Winchester         | MA    |          |         |

## ASSIGNEE-INFORMATION:

| NAME          | CITY      | STATE | ZIP CODE | COUNTRY | TYPE CODE |
|---------------|-----------|-------|----------|---------|-----------|
| Mitotix, Inc. | Cambridge | MA    |          |         | 02        |

APPL-NO: 8/ 767942 [PALM]  
DATE FILED: December 17, 1996

## PARENT-CASE:

RELATED APPLICATIONS This application is a continuation application of Ser. No. 08/486,663 filed on Jun. 7, 1995, pending. The contents of the aforementioned application is hereby incorporated by reference. This application is a continuation-in-part of U.S. Ser. No. 08/250,795, entitled "Immunosuppressant Target Proteins", filed on May 27, 1994 and is a continuation-in-part of U.S. Ser. No. 08/305,520, now U.S. Pat. No. 5,744,343 entitled "Ubiquitin Conjugating Enzymes", filed on Sep. 13, 1994 which is a continuation-in-part of U.S. Ser. No. 08/247,904, entitled "Human Ubiquitin Conjugating Enzyme", which is a continuation-in-part of U.S. Ser. No. 08/176,937 now abandoned, entitled "Assay and Reagents for Detecting Inhibitors of Ubiquitin-dependent Degradation of Cell Cycle Regulatory Proteins", filed on Jan. 4, 1994 the specification of which are incorporated by reference herein.

INT-CL: [7] G01 N 33/53

US-CL-ISSUED: 435/7.21; 435/29, 435/4, 435/6, 435/7.1, 435/23, 435/69.1, 435/7.2, 435/193, 530/350

US-CL-CURRENT: 435/7.21; 435/193, 435/23, 435/29, 435/4, 435/6, 435/69.1, 435/7.1, 435/7.2, 530/350

FIELD-OF-SEARCH: 435/4, 435/6, 435/7.1, 435/7.21, 435/23, 435/29, 435/69.1, 435/193, 435/7.2, 530/350

PRIOR-ART-DISCLOSED:

**WEST**

L14: Entry 26 of 55

File: USPT

Feb 15, 2000

US-PAT-NO: 6025480

DOCUMENT-IDENTIFIER: US 6025480 A

TITLE: Isolated nucleic acid molecules encoding P57KIP2

DATE-ISSUED: February 15, 2000

## INVENTOR-INFORMATION:

| NAME           | CITY     | STATE | ZIP CODE | COUNTRY |
|----------------|----------|-------|----------|---------|
| Massague; Joan | New York | NY    |          |         |
| Lee; Mong-Hong | New York | NY    |          |         |

## ASSIGNEE-INFORMATION:

| NAME  | CITY     | STATE | ZIP CODE | COUNTRY | TYPE | CODE |
|---|----------|-------|----------|---------|------|------|
| Sloan-Kettering Institute for Cancer Research | New York | NY    |          |         | 02   |      |

APPL-NO: 8/ 415655 [PALM]

DATE FILED: April 3, 1995

INT-CL: [7] C07 M 21/02, C02 H 21/04, C12 N 15/70, C12 N 1/21

US-CL-ISSUED: 536/23.1; 536/22.1, 536/24.31, 536/24.33, 435/24.02, 435/320.1

US-CL-CURRENT: 536/23.1; 435/320.1, 435/325, 435/348, 536/22.1, 536/24.31, 536/24.33

FIELD-OF-SEARCH: 536/22.1, 536/23.1, 536/24.3, 536/24.31, 536/24.33, 435/240.2, 435/320.1

PRIOR-ART-DISCLOSED:

## U.S. PATENT DOCUMENTS

| PAT-NO         | ISSUE-DATE | PATENTEE-NAME | US-CL    |
|----------------|------------|---------------|----------|
| <u>4683195</u> | July 1987  | Mullis        | 435/6    |
| <u>4683202</u> | July 1987  | Mullis        | 435/6    |
| <u>4745051</u> | May 1988   | Smith et al.  | 435/68   |
| <u>5302706</u> | April 1994 | Smith         | 536/23.1 |

## OTHER PUBLICATIONS

Ausebel, F.M. et al., (1992) "Manipulation of Yeast Genes," Short Protocols in Molecular Biology, John Wiley &amp; Sons, New York, 13-29 to 13-30 (Exhibit 5)

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L14: Entry 30 of 55 File: USPT Oct 19, 1999

US-PAT-NO: 5968761  
DOCUMENT-IDENTIFIER: US 5968761 A  
TITLE: Ubiquitin conjugating enzymes  
DATE-ISSUED: October 19, 1999

INVENTOR-INFORMATION:

| NAME                | CITY               | STATE | ZIP CODE | COUNTRY |
|---------------------|--------------------|-------|----------|---------|
| Rolfe; Mark         | Newton Upper Falls | MA    |          |         |
| Chiu; Maria Isabel  | Boston             | MA    |          |         |
| Cottarel; Guillaume | West Roxbury       | MA    |          |         |
| Berlin; Vivian      | Dunstable          | MA    |          |         |
| Damagnez; Veronique | Cambridge          | MA    |          |         |
| Draetta; Giulio     | Winchester         | MA    |          |         |

ASSIGNEE-INFORMATION:

| NAME          | CITY      | STATE | ZIP CODE | COUNTRY | TYPE CODE |
|---------------|-----------|-------|----------|---------|-----------|
| Mitotix, Inc. | Cambridge | MA    |          |         | 02        |

APPL-NO: 8/ 486663 [PALM]  
DATE FILED: June 7, 1995

PARENT-CASE:  
RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No. 08/250,795, filed May 27, 1994 entitled "Immunosuppressant Target Proteins", and is a continuation-in-part of U.S. Ser. No. 08/305,520, filed Sep. 13, 1994, now U.S. Pat No. 5,744,343, entitled "Ubiquitin Conjugating Enzymes", which is a continuation-in-part of U.S. Ser. No. 08/247,904, filed May 23, 1994 entitled "Human Ubiquitin Conjugating Enzyme", which is a continuation-in-part of U.S. Ser. No. 08/176,937, filed Jan. 4, 1994 now abandoned, entitled "Assay and Reagents for Detecting Inhibitors of Ubiquitin-dependent Degredation of Cell Cycle Regulatory Proteins", the specification of which are incorporated by reference herein.

INT-CL: [6] C12 Q 1/48, C12 N 9/10

US-CL-ISSUED: 435/15; 435/193  
US-CL-CURRENT: 435/15; 435/193

FIELD-OF-SEARCH: 435/15, 435/193

PRIOR-ART-DISCLOSED:

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L14: Entry 32 of 55 File: USPT Sep 28, 1999

US-PAT-NO: 5958769  
DOCUMENT-IDENTIFIER: US 5958769 A  
TITLE: Compositions and methods for mediating cell cycle progression  
DATE-ISSUED: September 28, 1999

INVENTOR-INFORMATION:  
NAME CITY STATE ZIP CODE COUNTRY  
Roberts; James M. Seattle WA  
Coats; Steven R. Seattle WA  
Fero; Matthew L. Seattle WA

ASSIGNEE-INFORMATION:  
NAME CITY STATE ZIP CODE COUNTRY TYPE CODE  
Fred Hutchinson Cancer Research Center Seattle WA 02

APPL-NO: 8/ 588595 [PALM]  
DATE FILED: January 18, 1996

INT-CL: [6] C12 N 15/79, C12 N 5/10, A01 N 43/04, C07 H 21/04

US-CL-ISSUED: 435/375; 435/325, 435/320.1, 514/44, 536/23.1, 536/24.5  
US-CL-CURRENT: 435/375; 435/320.1, 435/325, 514/44, 536/23.1, 536/24.5

FIELD-OF-SEARCH: 435/240.2, 435/240.26, 435/325, 435/375, 435/320.1, 424/93.21, 536/23.1, 536/24.5, 514/44

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

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|         |            |               |          |
|---------|------------|---------------|----------|
| PAT-NO  | ISSUE-DATE | PATENTEE-NAME | US-CL    |
| 5302706 | April 1994 | Smith         | 536/23.1 |

OTHER PUBLICATIONS

Rojanasakul, Y. Advanced Drug Delivery Reviews. 18:115-131, 1996.  
Stull, RA et al. Pharmaceutical Research. 12(4):465-483, 1995.  
Rivard, N et al. J. Biol. Chem. 27(31): 18337-18341, Aug. 2, 1996.  
Ravitz, MJ et al. Cancer Res. 55: 1413-1416, Apr. 1, 1995.  
Firpo, EJ et al. Mol. Cell Biol. 14(7); 4889-4901, Jul. 1994.  
Polyak, K et al. Cell. 78: 59-66, Jul. 15, 1994.  
Sorrentino, BP et al. Science. 257: 99-103, Jul. 3, 1992

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L14: Entry 41 of 55 File: USPT Nov 18, 1997

US-PAT-NO: 5688665  
DOCUMENT-IDENTIFIER: US 5688665 A

TITLE: Isolated nucleic acid molecules encoding the p27 KIP-1 protein  
DATE-ISSUED: November 18, 1997

INVENTOR-INFORMATION:

| NAME              | CITY     | STATE | ZIP CODE | COUNTRY |
|-------------------|----------|-------|----------|---------|
| Massague; Joan    | New York | NY    |          |         |
| Roberts; James M. | Seattle  | WA    |          |         |
| Koff; Andrew      | New York | NY    |          |         |
| Polyak; Kornelia  | New York | NY    |          |         |

ASSIGNEE-INFORMATION:

| NAME  | CITY     | STATE | ZIP CODE | COUNTRY | TYPE | CODE |
|---|----------|-------|----------|---------|------|------|
| Fred Hutchinson Cancer Research Center        | Seattle  | WA    |          |         |      | 02   |
| Sloan-Kettering Institute for Cancer Research | New York | NY    |          |         |      | 02   |

APPL-NO: 8/ 275983 [PALM]  
DATE FILED: July 15, 1994

PARENT-CASE:  
This application is a continuation-in-part of U.S. Ser. No. 08/179,045, filed Jan. 7, 1994, now abandoned.

INT-CL: [6] C12 N 15/12, C12 N 5/10, C12 N 1/21

US-CL-ISSUED: 435/69.2; 435/320.1, 435/252.3, 435/240.1, 536/23.5, 935/11  
US-CL-CURRENT: 435/69.2; 435/252.3, 435/320.1, 536/23.5

FIELD-OF-SEARCH: 435/69.1, 435/69.2, 435/240.2, 435/320.1, 435/252.3, 536/23.5, 935/70, 935/71, 935/11

PRIOR-ART-DISCLOSED:

OTHER PUBLICATIONS

Polyak et al. Genes and Develop. 8 (1994):9-22.  
Tempst et al. Electrophoresis 11 (1990): 537-553.  
Statagene 1991 Product Catalog.  
Deng et al. (1990), "A Novel Expression Vector for High-Level Synthesis and Secretion of Foreign proteins in Escherichia Coli: Overproduction of Bovine Pancreatic Phospholipase A2," Gene, vol 93: 229-234.  
Harper et al. (1993), "The p21 Cdk-Interacting Protein Cip1 is a Potent Inhibitor of G1 Cyclin-dependent Kinases," Cell vol. 75: 805-816.  
Koff et al. (1992), "Formation and Activation of a Cyclin E-cdk2 Complex During the

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L14: Entry 42 of 55

File: USPT

Sep 30, 1997

US-PAT-NO: 5672508

DOCUMENT-IDENTIFIER: US 5672508 A

TITLE: Inhibitors of cell-cycle progression, and uses related thereto

DATE-ISSUED: September 30, 1997

## INVENTOR-INFORMATION:

| NAME          | CITY           | STATE | ZIP CODE | COUNTRY |
|---------------|----------------|-------|----------|---------|
| Gyuris; Jeno  | Winchester     | MA    |          |         |
| Lamphere; Lou | Boston         | MA    |          |         |
| Beach; David  | Huntington Bay | NY    |          |         |

## ASSIGNEE-INFORMATION:

| NAME          | CITY      | STATE | ZIP CODE | COUNTRY | TYPE CODE |
|---------------|-----------|-------|----------|---------|-----------|
| Mitotix, Inc. | Cambridge | MA    |          |         | 02        |

APPL-NO: 8/ 589981 [PALM]

DATE FILED: January 23, 1996

INT-CL: [6] C12 N 15/62, C07 H 21/04

US-CL-ISSUED: 435/320.1; 536/23.4, 536/23.5

US-CL-CURRENT: 435/320.1; 536/23.4, 536/23.5

FIELD-OF-SEARCH: 424/93.1, 424/204.1, 424/450, 435/5, 435/6, 435/69.1, 435/235.1, 435/240.1, 435/254.2, 435/320.1, 435/240.4, 514/44, 536/23.4, 536/23.5

PRIOR-ART-DISCLOSED:

## FOREIGN PATENT DOCUMENTS

| FOREIGN-PAT-NO | PUBN-DATE      | COUNTRY | US-CL |
|----------------|----------------|---------|-------|
| WO 94/09135    | April 1994     | WOX     |       |
| WO 95/25429    | September 1995 | WOX     |       |
| WO 95/28483    | October 1995   | WOX     |       |

## OTHER PUBLICATIONS

Elledge, S. J. et al. (1994) "Cdk inhibitors: on the threshold of checkpoints and development" Curr Opin Cell Biol, vol. 6, pp. 847-852.

Guan K-L et al. (1994) "Growth suppression by p18, a p16 .sup.INK4/MTS1 and p14.sup.INK4B/MTS2 related cdk6 inhibitor correlates with wild-type pRb function" Genes & Dev. vol. 8, pp. 2939-2952.

Hannon G. and Beach D. (1994) "p15.sup.INK4B is a potential effector of TGF-.beta.-induced cell cycle arrest" Nature, vol. 371, pp. 257-261.

Harper J. et al (1994) "The p21 cdk-interaction"

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L14: Entry 49 of 55

File: EPAB

Jul 24, 1997

PUB-NO: WO009726327A1  
DOCUMENT-IDENTIFIER: WO 9726327 A1  
TITLE: COMPOSITIONS AND METHODS FOR MEDIATING CELL CYCLE PROGRESSION  
PUBN-DATE: July 24, 1997

INVENTOR-INFORMATION:

| NAME             | COUNTRY |
|------------------|---------|
| ROBERTS, JAMES M | US      |
| COATS, STEVEN R  | US      |
| FERO, MATTHEW L  | US      |

ASSIGNEE-INFORMATION:

| NAME                       | COUNTRY |
|----------------------------|---------|
| HUTCHINSON FRED CANCER RES | US      |
| ROBERTS JAMES M            | US      |
| COATS STEVEN R             | US      |
| FERO MATTHEW L             | US      |

APPL-NO: US09700831  
APPL-DATE: January 17, 1997

PRIORITY-DATA: US55859596A (January 18, 1996), US65656296A (May 31, 1996), US58859596A (January 18, 1996)

INT-CL (IPC): C12 N 5/04; C12 N 5/06; C07 H 21/00  
EUR-CL (EPC): C07K014/47; C12N015/82

ABSTRACT:

CHG DATE=19990617 STATUS=O>Hypercellular nonhuman organisms have functionally inactivated expression of a cyclin inhibitor gene, especially p27. The growth rate of nonhuman organisms are increased such that a desired size is attained more quickly than as compared to nonvariant organisms. Inhibitors of the p27 cyclin dependent kinase inhibitor protein or sequences encoding the protein modulate vertebrate cell cycle progression and increase the proportion of dividing cells to non-dividing cells in a population of treated cells. As the proportion of dividing cells increases, the cell population, e.g., hematopoietic progenitor (stem) cells, is more efficiently used for gene therapy applications. Transgenic animals and plants, and knockout alleles are provided.

091708 276  
RH#6

1. Document ID: US 20020006663 A1

Aug 2, 2001

L14: Entry 1 of 55

File: PGPB

Jan 17, 2002

DOCUMENT-IDENTIFIER: US 20020006663 A1  
TITLE: p27 and p21 in gene therapies

Abstract Paragraph (1):

The expansion of a population of stem cells or progenitor cells, or precursors thereof, may be accomplished by disrupting or inhibiting p21.sup.cip1/waf1 and/or p27, cyclin dependent kinase inhibitors. In the absence of p27 activity, progenitor cells move into the cell cycle and proliferate; whereas in the absence of p21 activity, stem cells move into the cell cycle and proliferate without losing their pluripotentiality (i.e., their ability to differentiate into the various cell lines found in the blood stream). Any type of stem cell or progenitor cell, or precursor thereof, including, but not limited to, hematopoietic, gastrointestinal, lung, neural, skin, muscle, cardiac muscle, renal, mesenchymal, embryonic, fetal, or liver cell may be used in accordance with the invention. The present invention provides a method of expanding a cell population, cells with decreased p27 and/or p21 activity, transgenic animals with a disrupted p27 and/or p21 gene, pharmaceutical compositions comprising the cells of the invention, and methods of using these cells in gene therapy (e.g., stem cell gene therapy) and bone marrow transplantation.

DOCUMENT-IDENTIFIER: US 20010011076 A1  
TITLE: COMBINATIONS OF PKC INHIBITORS AND THERAPEUTIC AGENTS FOR TREATING CANCERS

Detail Description Paragraph (172):

[0203] (iii) To examine in vitro cdk2 and to identify other related cell cycle dependent proteins associated with the induction of apoptosis and the inhibition of PKC: The basis for the increase in cdk2 activity by safingol and MMC in combination remains unknown. It may be related to a decrease in the expression of a cdk2 inhibitor (i.e. p21) or it may be related to a modification of a phosphorylated site on cdk2 which results in its activation. A further understanding of this process may lead to new surrogate markers of activity. In order to examine this further applicants plan to examine: 1) protein expression of p21 and p27 with immunoblotting using an enhanced chemiluminescence system using specific antibodies (Santa Cruz Biotechnology, Inc. Santa Cruz, Calif.); 2) differences in protein phosphorylation of cdk2 with [.sup.32P]orthophosphate cell labelling, as previously described, using a cdk2 specific antibody suitable for immunoprecipitating (36); and 3) correlative studies of cdk2 activity as measured by the histone H1 kinase assays (38). Control cells will be treated in the same way as described above except that standard media without drug will be used for all incubations.

4. Document ID: US 20010006974 A1

L14: Entry 4 of 55

File: PGPB

Jul 5, 2001

DOCUMENT-IDENTIFIER: US 20010006974 A1  
TITLE: COMBINATION THERAPY FOR LYMPHOPROLIFERATIVE DISEASES

Detail Description Paragraph (1):

[0041] Treatment according to the invention has occurred through an ongoing phase I clinical trial performed at Walter Reed Army Medical Center and The Johns Hopkins Oncology Center. In this study, patients with low-grade lymphoproliferative disorders have been treated using the combination of theophylline (dosed to a serum level of 10-20 ug/ml) on days 1-9, pentostatin 2-4 mg/m2 day 8 and chlorambucil 20 mg/m2 day 8. Assessment of in vivo modulation of bcl-2 (whose over-expression correlates with drug resistance and poor outcome in CLL) and p27 occurred at the pre-treatment, day 3, day 8, day 9 and day 15 of treatment.

2. Document ID: US 20020006628 A1

L14: Entry 2 of 55

File: PGPB

Jan 17, 2002

DOCUMENT-IDENTIFIER: US 20020006628 A1  
TITLE: Methods of diagnosing and monitoring endometrial glandular development

Detail Description Paragraph (17):

[0080] It has been discovered that the expression patterns and cellular localization of the cellular protein cyclin E can be used as a marker to evaluate endometrial glandular development during the menstrual cycle. This marker is particularly useful when used in combination with the marker p27 and/or MAG and/or progesterone receptors. By detecting expression levels and cellular localization of markers at different time points in the menstrual cycle useful information can be gleaned and used in the diagnosis and treatment of patients being evaluated and treated for various conditions and disorders.

5. Document ID: US 6335170 B1

L14: Entry 5 of 55

File: USPT

Jan 1, 2002

3. Document ID: US 20010011076 A1

L14: Entry 3 of 55

File: PGPB

DOCUMENT-IDENTIFIER: US 6335170 B1  
TITLE: Gene expression in bladder tumors

Detailed Description Paragraph Table (102):

84 20 20 20 20 X64877\_at 25 20 20 38 20 88 X64877\_s\_at H. sapiens mRNA for serum protein 20 20 20 20 20 X64878\_at H. sapiens mRNA for oxytocin receptor 20 20 20 20 24 20 X64994\_at H. sapiens HGMP071 gene for olfactory receptor 39 61 35 90 20 32 X65233\_at H. sapiens mRNA for Zinc-finger protein (ZNFpT17) 20 27 20 20 39 20 X65293\_at H. sapiens mRNA for protein kinase C-Epsilon 20 20 20 20 20 X65463\_at H. sapiens mRNA for MHC class I promoter binding protein 40 20 20 20 20 X65488\_at H. sapiens U21.1 mRNA 81 94 414 307 129 102 X65550\_at H. sapiens mki67a mRNA (long type) for antigen of monoclonal antibody Ki-67 20 25 20 20 30 55 X65614\_at H. sapiens mRNA for calcium-binding protein S100P 687 4027 3566 3068 3376 2249 X65633\_at H. sapiens ACTH-R gene for adrenocorticotrophic hormone receptor 62 78 27 32 22 61 X65644\_at H. sapiens mRNA MBP-2 for MHC binding protein 2 42 20 68 56 20 20 X65663\_at H. sapiens Sox-6 mRNA. /gb=X65663 /ntype=RNA 20 24 20 20 52 21 X65724\_at H. sapiens DNA for ORF1 and ORF2 from chromosome X 20 33 20 22 30 79 X65727\_cds2\_s\_at GSTAlfa locus gene (glutathione S-transferase) extracted from H. sapiens GSTAlfa gene for glutathione S-transferase exon 2 20 27 34 20 110 85 X65784\_s\_at H. sapiens CAR gene 21 87 47 46 20 54 X65857\_at H. sapiens HGMP07E gene for olfactory receptor 28 20 74 20 173 44 X65867\_at H. sapiens mRNA for adenylosuccinate lyase 20 20 25 30 20 24 X65873\_at H. sapiens mRNA for kinesin (heavy chain) 100 52 56 71 70 115 X65962\_s\_at H. sapiens mRNA for cytochrom P-450 28 66 99 84 181 20 X65965\_s\_at H. sapiens SOD-2 gene for manganese superoxide dismutase. /gb=X65965 /ntype=DNA /annot=exon 112 209 45 115 104 123 X65977\_at H. sapiens mRNA for corticostatin HP-4 precursor 20 20 20 20 20 X66079\_at H. sapiens Spi-B mRNA 128 70 108 78 47 103 X66087\_at H. sapiens a-myb mRNA 23 41 20 21 293 20 X66113\_s\_at H. sapiens mRNA for PM/Sci 100kD nucleolar protein 20 49 63 44 20 65 X66114\_mal\_at H. sapiens gene for 2-oxoglutarate carrier protein. 20 34 31 20 20 84 X66141\_at H. sapiens mRNA for cardiac ventricular myosin light chain-2 54 79 82 42 34 127 X66142\_s\_at H. sapiens mRNA for rod cGMP phosphodiesterase 64 117 214 108 20 44 X66171\_at H. sapiens CMRF35 "mRNA," complete CDS 20 20 20 20 20 X66276\_s\_at H. sapiens mRNA for skeletal muscle C-protein 20 38 76 37 20 45 X66358\_at H. sapiens mRNA KKIALLRE for serine/threonine protein kinase 20 20 20 20 22 20 X66360\_at H. sapiens mRNA PCTAIRE-2 for serin/threonine protein kinase 20 20 20 20 20 20 X66362\_at H. sapiens mRNA PCTAIRE-3 for serine/threonine protein kinase 50 53 54 47 164 20 X66363\_at H. sapiens mRNA PCTAIRE-1 for serine/threonine protein kinase 84 138 26 69 311 254 X66364\_at H. sapiens mRNA PSSALRE for serine/threonine protein kinase 80 91 98 112 150 198 X66365\_at H. sapiens mRNA PLSTIRE for serin/threonine protein kinase 25 20 45 31 20 26 X66397\_at H. sapiens trp mRNA 62 92 130 111 98 99 X66401\_cds1\_at H. sapiens genes TAP1, TAP2, LMP2, LMP7 and DOB. 90 188 70 38 73 205 X66403\_at H. sapiens mRNA for acetylcholine receptor (epsilon subunit) 41 52 25 32 25 20 X66417\_at H. sapiens casK mRNA for kappe-casein 66 57 79 45 86 200 X66436\_at H. sapiens hsr1 mRNA (partial) 51 128 159 76 138 243 X66503\_at Human adenylosuccinate synthetase mRNA 20 42 56 52 20 31 X66533\_at H. sapiens soluble guanylate cyclase small subunit mRNA 20 45 20 20 20 42 X66534\_at H. sapiens soluble guanylate cyclase large subunit mRNA 20 20 20 20 20 X66610\_at H. sapiens mRNA for enolase 20 27 20 20 51 38 X66785\_at H. sapiens mRNA for transactylase (DBT) 105 408 588 266 926 274 X66839\_at H. sapiens MaTu MN mRNA for p54/58N protein 32 89 101 140 163 161 X66867\_cds1\_at H. sapiens max gene 40 20 26 24 28 20 X66894\_s\_at H. sapiens FACC mRNA from complementatin group C (FA(C)) 20 76 84 48 112 54 X66899\_at H. sapiens EWS mRNA 35 20 164 77 20 51 X66922\_at H. sapiens mRNA for myo-inositol monophosphatase 20 20 20 20 20 X66945\_at H. sapiens N-sam mRNA for

fibroblast growth factor receptor 59 33 20 20 20 20 X67081\_at H. sapiens histone H4 gene 20 20 20 20 20 X67098\_at H. sapiens rTS alpha mRNA containing four open reading frames 20 20 51 27 23 20 X67155\_at H. sapiens mRNA for mitotic kinesin-like protein-1 34 71 23 23 41 20 X67235\_s\_at H. sapiens mRNA for proline rich homeobox (Prh) protein 20 35 20 20 20 20 X67247\_mal1\_at H. sapiens rpS8 gene for ribosomal protein S8. 3725 3402 3977 3818 1511 2083 X67318\_at H. sapiens mRNA for procaryboxypeptidase A1 20 20 20 20 20 X67325\_at H. sapiens p27 mRNA 102 194 64 20 20 893 X67337\_at H. sapiens HPBRII-4 mRNA 20 25 20 20 20 20 X67491\_f at H

sapiens gene for glutamate dehydrogenase 27 20 20 61 20 20 X67594\_at H. sapiens mRNA for MSH receptor 20 20 20 20 20 X67683\_at H. sapiens mRNA for keratin 4 /gb=X67683 /ntype=RNA 2126 161 114 106 268 189 X67697\_at H. sapiens HE2 mRNA 87 36 56 46 172 57 X67698\_at H. sapiens tissue specific mRNA 401 372 388 322 265 472 X67734\_at H. sapiens mRNA for transient axonal glycoprotein (tag-1) 20 20 20 33 56 20 X67951\_at H. sapiens mRNA for proliferation-associated gene (pag) 1472 608 647 646 543 814 X68090\_s\_at H. sapiens Fc-gamma-RIIA gene for IgG Fc receptor class IIA (5'flank). /gb=X58090 /ntype=DNA /annot=CDS 20 20 20 133 20 X68149\_at H. sapiens BLRI gene for Burkitt's lymphoma receptor 1 20 20 20 20 X68194\_at H. sapiens h-Sp1 mRNA 42 31 124 101 20 21 X68242\_at H. sapiens mRNA for Hin-1 20 20 20 20 20 X68264\_mal1\_at H. sapiens MGF gene exons 1&2. 20 20 20 20 20 X68277\_at H. sapiens CL 100 mRNA for protein tyrosine phosphatase 1972 105 44 42 74 198 X68285\_s\_at H. sapiens mRNA for glycerol kinase 20 20 32 20 20 20 X68314\_at H. sapiens mRNA for glutathione peroxidase-G1 380 739 734 1019 386 293 X68486\_at H. sapiens mRNA for A2a adenosine receptor 134 121 145 117 41 77 X68487\_at H. sapiens mRNA for A2b adenosine receptor 22 20 34 20 20 X68505\_s\_at 27 31 20 25 20 20 X68560\_at H. sapiens SPR-2 mRNA for GT box binding protein 78 55 51 44 40 94 X68561\_at H. sapiens SPR-1 mRNA for FT box binding protein 20 20 23 22 20 20 X68688\_mal1\_s\_at H. sapiens ZNF33B gene 20 20 48 20 262 227 X68733\_mal1\_at H. sapiens gene for alpha1-antichymotrypsin, exon 1. 142 185 98 97 92 174 X68742\_at H. sapiens mRNA for "integrin," alpha subunit 20 49 20 20 42 35

Detailed Description Paragraph Table (120):

X04347\_s\_at HSUPIR1 liver mRNA fragment DNA bindin log pos X04347\_s\_at HSUPIR1 liver mRNA fragment DNA bindin log pos X06814\_at HSRRA receptor of retinoic acid. :r log pos X06617\_at HSRPS11 ribosomal protein S11. : ribo log pos X06985\_at HSOXYGR heme oxygenase. :heme oxygena log pos X06985\_at HSOXYGR heme oxygenase. :heme oxygena log pos X07696\_at HSKERC15 cytokeratin 15. :keratin 15: log pos X07730\_at HSPSA prostate specific antigen.: log pos X07730\_at HSPSA prostate specific antigen.: log pos X12447\_at HSALDOA aldolase A gene (EC 4.1.2.13 log pos X12671\_mal1\_at HSHNRNPA gene for heterogeneous nuclear log pos X12671\_mal1\_at HSHNRNPA gene for heterogeneous nuclear log pos X12876\_s\_at HSKER18A mRNA fragment for cytotkeratin log pos X12876\_s\_at HSKER18A mRNA fragment for cytotkeratin log pos X13334\_at HSCD14R CD14 myelid cell-specific leu log pos X13546\_mal1\_at HSHMG17G HMG-17 gene for non-histone cn log pos X13794\_mal1\_at HSLDHB1 lactate dehydrogenase B gene e log pos X13794\_mal1\_at HSLDHB1 lactate dehydrogenase B gene e log pos X14008\_mal1\_f at HSLYSOZY lysozyme gene (EC 3.2.1.17). log pos X15940\_at HSRPL31 ribosomal protein L31. :ribos log pos X16084\_at HSTUMP translationally controlled tu log pos X16832\_at HSCATHH cathepsin H (EC 3.4.22.16). log pos X17042\_at HSHPCP hematopoietic proteoglycan cor log pos X17206\_at HSLLEP3 LLRep3. : LLRep3 log pos X51345\_at HSJUNB jun-B JUN-B protein. :jun B p log pos X51466\_at HSEF2 elongation factor 2. : elonga log pos X51688\_at HSCYCLINA cyclin A. log pos X52003\_at HSPS2MKN p52 protein gene. :trefoil fac log pos X52003\_at HSPS2MKN P52 protein gene. :trefoil fac log pos X52426\_s\_at HSCYTK cytokeratin 13. : cytokeratin log pos X52426\_s\_at HSCYTK cytokeratin 13. : cytokeratin log pos X52851\_mal1 at HSCPH70 cyclophilin gene for cyclophil log pos X52966\_at HSL35A ribosomal protein L35a. :ribo log pos X53588\_mal1 at HSINTA6R integrin alpha 8. :integrin, log pos X53587\_at HSINTB4R integrin beta 4. : integrin b log pos X53777\_at HSL23MR L23 putative ribosomal protei log pos X54232\_at HSGLYPIC heparan sulfate proteaglycan log pos X54867\_at HSCYSTATS cystatin S. log pos X54942\_at HSCSKSHS2 ckshs2 Cks1 protein homologue log pos X54942\_at HSCSKSHS2 ckshs2 Cks1 protein homologue log pos X55005\_mal1 at HSCERBAR c-erbA-1 thyroid hormone rece log pos XS5715\_at HSHUMS3 Hums3 40S ribosomal protein s log pos X55954\_at HSL17ARP HSL23 ribosomal protein homolo log pos X56494\_at HSPKM12 M gene for M1-type and M2-type log pos X56887\_s\_at HSAUTNOR autoantigen NOR-90. log pos X56807\_at HSDGII DSC2 desmocollins type 2a and log pos X58841 at HSHLAE HLA-E gene. :major histocompat log pos X56932\_at HS23KDHPB 23 kD highly basic protein. log pos X57351 at HS18D 1-8D gene from interferon induc log pos X57351 at HS18D 1-8D gene from

interferon-indu log pos X57351\_s at HS18D 1-8D gene from interferon-indu  
log pos X57809\_s at HSGVVL009 rearranged immunoglobulin  
lamb log pos X57809\_s at HSGVVL009 rearranged immunoglobulin lamb log  
pos X57959\_at HSRBPR7A ribosomal protein L7. :riboso log  
pos X58072\_at HSGATA3R hGATA3 trans-acting T-cell sp log pos  
X59373\_at HSHOX4D HOX4D a homeobox protein. :ho log pos X59798\_at  
HSRAD1CY PRAD1 cyclin. :PRAD1 cyclin log pos X80489\_at HSEF1B  
elongation factor-1-beta. log pos X61587\_at HSRHOG rhoG GTPase.  
:ras homolog gen log pos X82320\_at HSEPIT1 epithelin 1 and 2. : epitheli  
log pos X82468\_at HSCAMPAT1 CAMPATH-1 (CDw52) antigen.  
log pos X62468\_at HSCAMPAT1 CAMPATH-1 (CDw52) antigen. log pos  
X62854\_ma1 at HSMCEDAG gene for Me491/CD63 antigen.: log pos  
X62891\_at HSRPRNA ribosomal protein (homologuo log pos X63359\_at  
HSUGT2BIO UGT2BIO udp glucuronosyltrans log pos X83527\_at  
HSRPL19 ribosomal protein L19. :ribos log pos X83629\_at HSPCAD p  
cadherin. :cadherin 3, P-ca log pos X84229\_at HSDEK9 dek mRNA.  
:DEK gene log pos X64707\_at HSBBC1 BBC1 mRNA. log pos X65814\_at  
HSS100PCB calcium-binding protein S100P log pos X68114\_ma1 at  
HS2OXOC gene for 2-oxoglutarate carrie log pos X88383\_at HSSTHPKD  
mRNA PCTAIRE-1 for serine/thre log pos X66363\_at HSSTHPKD mRNA  
PCTAIRE-1 for serine/thre log pos X88899\_at HSEWS EWS mRNA.  
:Ewing sarcoma break log pos X87247\_ma1 at HSRPS8 rpS8 gene for  
ribosomal protei log pos X87325\_at H5P27 p27 mRNA. :interferon, alpha-1  
log pos X87951\_at HSPAG proliferation-associated gene log  
pos X68314\_at HSGPGI glutathione peroxidase-GI. :g log pos X68314\_at  
HSGPGI glutathione peroxidase-GI. :g log pos X68688\_ma1\_s at  
HSZNB ZNF33B gene. log pos X89150\_at HSRPS18 ribosomal protein S18.  
:ribos log pos X69391\_at HSRPL6AA ribosomal protein L6.  
:riboso log pos X89550\_at HSRHO1 rho GDP-dissociation Inhibito log pos  
X69854\_at HSS26 ribosomal protein S26. log pos X70940\_s at  
HSEFAC1A2 elongation factor 1 alpha-2. log pos X70940\_s at  
HSEFAC1A2 elongation factor 1 alpha-2. log pos X73079\_at HSPIR  
encoding  
Polymeric immunogloblu log pos X73358\_s at HSAESI hAES-1 mRNA.  
:amino-terminal e log pos X73460\_at HSRPL3A ribosomal protein L3.  
log pos X73478\_at HSPTPAA hPTPA mRNA. :hPTPA mRNA log pos  
X74819\_at HSCARTROT cardiac troponin T. log pos X74819\_at  
HSCARTROT  
cardiac troponin T. log pos X74929\_s at HSKRT8 KRT8 keratin 8. :keratin  
8 :K log pos X75252\_at HSPEABP phosphatidylethanolamine  
bindi log pos X76534\_at HSNMB NMB mRNA. :transmembrane glyco log  
pos X76534\_at HSNMB NMB mRNA. :transmembrane glyco log pos  
X77794\_at HSCYCG1 cyclin G1. :cyclin G1 log pos X78992\_at HSERF2  
ERF-2 mRNA. log pos X79234\_at HSRPL11 ribosomal protein L11. log  
pos X79439\_at HSNOTCH3 Notch 3 DNA sequence. :Notch log pos  
X80062\_at HSSAMRNA SA mRNA. log pos X80198\_at HSMLN64  
MLN64 mRNA. log  
pos X80200\_at HSMLN62 MLN62 mRNA. :TNF receptor-asso log pos  
X80822\_at HSPLORF ORF. log pos X80909\_at HSNAC alpha NAC  
mRNA.  
:nascent-polyp log pos X82893\_at HSE48 E48 antigen. : E48 antigen log pos  
X82693\_at HSE48 E48 antigen. : E48 antigen log pos  
X83418\_s at HSPRP2 PrP gene, exon 2. :Prp "gene log pos X83492\_at  
HSFAS47 Fas/Apo-1 (clone pCRTM11-Fas log pos X83492\_at HSFAS47  
Fas/Apo-1 (clone pCRTM11-Fas log pos X83572\_at HSARSD ARSD gene,  
complete CDS. :aryl log pos X88809\_at HSPEA15 major astrocytic  
phosphoprote log pos X87159\_at HSSCNN1B beta subunit of epithelial am  
log pos X87241\_at HSHFATPRO hFat protein. :FAT tumor supp  
log pos X89418\_at HSRNAPPP5 protein phosphatase 5. :prote log pos  
X89416\_at HSRNAPPP5 protein phosphatase 5. :prote log pos  
X90848\_at HARNAMLK2 mixed lineage kinase 2. log pos X91103\_at  
HSRNAHR44 Hr44 protein. log pos X93038\_at HSMAT82 MAT8 protein. :  
phospholemmann- log pos X94563\_xpt2\_r at HSDBIEX12 dbi/acbp gene  
exon 1 & 2. log pos X94612\_at HS2CGMPPK type. vertline. vertline.  
cGMP-dependent protei log pos X95404\_at HSNMCF1 non-muscle type  
cofilin. :cof log pos X95735\_at HSZYXIN2R zyxin. :zyxin log pos  
X95808\_s at HSDXS protein encoded by a candidat log pos X98482\_at  
HS.TNNTX11 TNNT2 gene exon 11. log pos X98482\_r at HSTNNTX11  
TNNT2 gene exon 11. log

L14: Entry 6 of 55

File: USPT

Nov 13, 2001

DOCUMENT-IDENTIFIER: US 6316435 B1

TITLE: Combination therapy for lymphoproliferative diseases

Detailed Description Paragraph Right (1):

Treatment according to the invention has occurred through an ongoing phase I clinical trial performed at Walter Reed Army Medical Center and The Johns Hopkins Oncology Center. In this study, patients with low-grade lymphoproliferative disorders have been treated using the combination of theophylline (dosed to a serum level of 10-20 ug/ml) on days 1-9, pentostatin 2-4 mg/m2 day 8 and chlorambucil 20 mg/m2 day 8. Assessment of in vivo modulation of bcl-2 (whose over-expression correlates with drug resistance and poor outcome in CLL) and p27 occurred at the pre-treatment, day 3, day 8, day 9 and day 15 of treatment.

7. Document ID: US 6316208 B1

L14: Entry 7 of 55

File: USPT

Nov 13, 2001

DOCUMENT-IDENTIFIER: US 6316208 B1

TITLE: Methods for determining isolated p27 protein levels and uses thereof

Detailed Description Paragraph Right (66):

The subject invention further provides a method for quantitatively determining the level of expression of p27 in a cell population, and a method for determining whether an agent is capable of increasing or decreasing the level of expression of p27 in a cell population. The method for determining whether an agent is capable of increasing or decreasing the level of expression of p27 in a cell population comprises the steps of (a) preparing cell extracts from control and agent-treated cell populations, (b) isolating p27 from the cell extracts (e.g., by affinity chromatography on, and elution from, a cyclin E-Cdk2 complex solid phase affinity adsorbent), (c) quantifying (e.g., in parallel) the amount of p27 inhibitor activity in the control and agent-treated cell extracts using a cyclin E-Cdk2 kinase assay (e.g., histone H1 assay described infra). Agents that induce increased p27 expression may be identified by their ability to increase the amount of p27 inhibitor activity in the treated cell extract in a manner that is dependent on transcription, i.e., the increase in p27 inhibitor activity is prevented when cells are also treated with an inhibitor of transcription (e.g., actinomycin D). In a similar manner, agents that decrease expression of p27 may be identified by their ability to decrease the amount of p27 inhibitor activity in the treated cell extract in a manner that is dependent upon transcription.

8. Document ID: US 6245965 B1

L14: Entry 8 of 55

6. Document ID: US 6316435 B1

File: USPT

Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245965 B1

TITLE: Knockout mice and cells that lack p19INK4d and p27KIP1 activity and methods of use thereof

Detailed Description Paragraph Right (6):

Since p27<sup>sup.KIP1</sup> single null animals develop tumors when challenged by gamma irradiation or when treated with chemicals such as DMBA that cause DNA breaks, the p27 is haplo-insufficient for tumor formation. Therefore the p19<sup>sup.INK4d</sup>-double null/p27<sup>sup.KIP1</sup>-single null can develop brain tumors or other malignancies since both genes are expressed ubiquitously in adult tissues. Such mice can be used as a model system for identifying agents that can be used in treating tumors.

9. Document ID: US 6245560 B1

L14: Entry 9 of 55

File: USPT

Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245560 B1

TITLE: Vector with multiple target response elements affecting gene expression

Detailed Description Paragraph Right (76):

TAR-Rib and DC vector-transduced Molt3 cells (1.times.10<sup>sup.8</sup> cells) were treated with 20 .mu.g DEAE-dextran, washed and infected with SIV-1.sub.mac251 at a low MOI (ID.sub.50 =0.5) for 2 hours at 37.degree. C. Cells were washed and maintained in RPMI 1640 containing 10% FCS. Supernatants were collected and assayed for SIV-1 p27 using an ELISA (Coulter). Up to 90% inhibition of SIV replication was observed in the TAR-Rib-transduced cells compared to the vector alone (FIG. 15). In addition, flow cytometry analysis using monoclonal antibodies to CD4 indicated that 92% of the SIV-infected, TAR-Rib-transduced cells expressed CD4 on their surface. In contrast, only 52% of the SIV-infected, DC vector-transduced cells expressed CD4. Thus, The TAR-Rib construct was able to protect cells against the loss of CD4. The inhibition of SIV replication and CD4 protection described above is only due to the 50 TAR elements, since the gag ribozyme has no specificity for SIV mRNA.

10. Document ID: US 6242575 B1

L14: Entry 10 of 55

File: USPT

Jun 5, 2001

DOCUMENT-IDENTIFIER: US 6242575 B1

TITLE: Antibodies for detecting p27 protein

Detailed Description Paragraph Right (60):

The subject invention further provides a method for quantitatively determining the level of expression of p27 in a cell population, and a method for determining whether an agent is capable of increasing or decreasing the level of expression of p27 in a cell population. The method for determining whether an agent is capable of increasing or decreasing the level of expression of p27 in a cell population comprises the steps of (a) preparing cell extracts from control and agent-treated cell populations, (b) isolating p27 from the cell extracts (e.g., by affinity chromatography on, and elution from, a cyclin E-Cdk2 complex solid phase affinity adsorbant), (c) quantifying (e.g., in parallel) the amount of p27 inhibitor activity in the control and agent-treated cell extracts using a cyclin E-Cdk2 kinase assay (e.g., histone H1 assay described infra). Agents that induce increased p27 expression may be identified by their ability to increase the amount of p27 inhibitor activity in the treated cell extract in a manner that is dependant on transcription, i.e., the increase in p27 inhibitor activity is prevented when cells are also treated with an inhibitor of transcription (e.g., actinomycin D). In a similar manner, agents that decrease expression of p27 may be identified by their ability to decrease the amount of p27 inhibitor activity in the treated cell extract in a manner that is dependent upon transcription.

11. Document ID: US 6225112 B1

L14: Entry 11 of 55

File: USPT

May 1, 2001

DOCUMENT-IDENTIFIER: US 6225112 B1

TITLE: Human p27Kip1 gene promoter

Detailed Description Paragraph Right (8):

The DNA to be used for the competitive inhibition usually has a length of at least 6 bases or more, and more preferably 10 bases or more. Examples of the DNA to be used for the competitive inhibition include sequences containing the consensus binding sites for the transcription factors described in FIG. 1 and FIG. 5. Since the p27 protein is known to stop the cellular proliferation, it would be effective to enhance the activity of the promoter DNA of the present invention for the treatment of proliferative cellular diseases, such as malignant tumors, arteriosclerosis, and restenosis caused by the endothelial proliferation after the balloon coronary angioplasty. On the other hand, the inhibition of the activity of the promoter DNA of the present invention would be effective for the treatment of diseases that require cellular proliferation, such as aplastic anemia, cirrhosis, or wound healing.

12. Document ID: US 6218146 B1

L14: Entry 12 of 55

File: USPT

Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218146 B1  
TITLE: MTS2 gene

Detailed Description Paragraph Right (213):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDKs. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDKs are protooncogenes and that P16 (MRS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

13. Document ID: US 6210949 B1

L14: Entry 13 of 55

File: USPT

Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6210949 B1  
TITLE: Mouse MTS2 gene

Detailed Description Paragraph Right (216):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have

also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the Cdk's. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or Cdk4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and Cdk's are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

14. Document ID: US 6203991 B1

L14: Entry 14 of 55

File: USPT

Mar 20, 2001

DOCUMENT-IDENTIFIER: US 6203991 B1  
TITLE: Inhibition of smooth muscle cell migration by heme oxygenase I

Drawing Description Paragraph Right (87):

Progression through the cell cycle is controlled by the assembly and disassembly of the different cyclin-cyclin dependent kinase complexes. These complexes phosphorylate retinoblastoma protein leading to the release of the sequestered transcription factors, E2F and Elf 1. The cyclin dependent kinase inhibitors (CKIs) modulate the enzymatic activity of cyclin/CDK complexes necessary for G.sub.1 progression. In vivo, Ad-p21 infection of porcine iliofemoral and rat carotid arteries following balloon injury reduces BrdU incorporation by 35% and I/M area ratio by 37%. Likewise, Gax homeobox gene overexpression, as an upstream regulator of p21, in the rat carotid artery injury model inhibited neointimal formation and luminal narrowing by 59 and 56 percent, respectively. Adenovirus-mediated overexpression of p27 in balloon-injured rat and porcine arteries significantly attenuated intimal lesion formation.

Drawing Description Paragraph Right (94):

The method of the present invention can be combined with other methods for treating cell proliferation. For example, other genes such as thymidine kinase, cytosine deaminase, p21, p27, and p53 and combinations thereof can be concomitantly transformed into cells and expressed. For example, the herpes simplex-thymidine kinase (HS-tK) gene, when delivered to blood vessel walls by a adenoviral vector system, successfully resulted in the decrease in neointimal proliferation associated with restenosis (Chang et al., Mol. Med., 1995, 172-181). In the context of the present invention, it is contemplated that HO1 gene expression could be used similarly in conjunction with other gene therapy approaches. The genes may be encoded on a single nucleic acid but separately transcribed. Alternatively, the genes may be operably linked such that they are cotranscribed. In preferred embodiments, the

genes are operably linked to encode a fusion protein. In other embodiments the co-transcribed genes are separated by an internal ribosome binding site allowing the proteins to be translated separately. Such combination therapies are described in WO 99/03508 (incorporated herein by reference in its entirety).

Detailed Description Paragraph Right (7):

The temporal and spatial expression pattern of HO1 after arterial injury in the pig concurs with the expression pattern of the cell cycle regulatory proteins, p21, p27, and p57 (Tanner et al., Circ. Res., 1997), suggesting that HO1/CO may play a role in the upstream transduction pathway leading to the expression of cyclin dependent kinase inhibitors and hence G1/G0 cell cycle arrest, exit and cell differentiation. Indeed, the lower regions of the neointima have also been associated by low vsmc mitogenesis and procollagen synthesis (Tanner et al., Circ. Res., 1997). Western blot analysis of arterial homogenates confirmed the immunohistological data. Although expression levels may vary between different animals, HO1 protein expression was lost directly after arterial injury and upregulated between day 7 and 21 post injury (pi) and correlated inversely to cell proliferation.

15. Document ID: US 6180776 B1

L14: Entry 15 of 55

File: USPT

Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180776 B1

TITLE: MTS2 gene

Detailed Description Paragraph Right (186):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdks may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdks (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al. 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDKs. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdks while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdks (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDKs are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of

their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

16. Document ID: US 6180643 B1

L14: Entry 16 of 55

File: USPT

Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180643 B1

TITLE: Aryl and heteroaryl substituted fused pyrrole antiinflammatory agents

Brief Summary Paragraph Right (6):

The above approaches block the effects of TNF- $\alpha$  and IL-1 by either protein sequestration or receptor antagonism, but an additional approach to blockade is to intervene in the cellular production and secretion of IL-1 and/or TNF. There are numerous points for intervention between the extracellular stimulus and the secretion of IL-1 and TNF- $\alpha$  from the cell including interfering with transcriptional processes, interfering with translational processes, blocking signal transduction which may alter protein translation and/or transcription; and blocking release of the proteins from the cells. The most reliable effect to document is upon applying a given stimulus to a cell in vitro (eg. monocyte), a certain amount of TNF or IL-1 (note: quantitated by enzyme linked immunoabsorbent assay, ELISA) is secreted over basal levels in the culture medium. Evidence as to the nature of intervention between the extracellular stimulus and the secretion of IL-1 and TNF- $\alpha$  from the cell can be provided by in vitro biochemical experiments, but it does not preclude the fact that the compounds may be intervening at a yet undetermined point on the pathway between extracellular stimulus and secretion of protein. Pentoxifylline is an example of a compound that is believed to intervene at the transcriptional level of IL-1 protein synthesis. Evidence suggests that the antiinflammatory glucocorticoids block at both the transcriptional and translational levels (Lee et al Circulatory Shock 44:97-103 (1995)) of inflammatory mediators. Chloroquine (CQ) and hydroxychloroquine (HCQ) accumulate in lysosomes of monocytes (Borne Handbook of Cardiovascular and Anti-Inflammatory Agents p27-104 (1986)). CQ and HCQ inhibit cartilage cathepsin B and cartilage chondromucoprotease, and they may have membrane stabilizing effects on the lysosomes.

Other Reference Publication (14):

Borne Handbook of Cardiovascular and Anti-Inflammatory Agents, p27-104 (1986).

17. Document ID: US 6177272 B1

L14: Entry 17 of 55

File: USPT

Jan 23, 2001

DOCUMENT-IDENTIFIER: US 6177272 B1

TITLE: Method for treating vascular proliferative diseases with p27 and

**Brief Summary Paragraph Right (7):**

Previous studies of these CKIs were focused on their potential role in malignant transformation. For example, PCT Publication No. WO95/18824 (applicant Sloan-Kettering Institute For Cancer Research) describes a method for identifying agents capable of modulating the ability of p27 to inhibit the activation of the cyclin E-Cdk2 complex. This PCT publication further provides methods for treating subjects diagnosed with a hyperproliferative disorder, such as cancer and hyperplasia, using these agents. Such agents can be both protein and non-protein moieties. Unfortunately, the involvement of CKIs in cardiovascular diseases, including atherosclerosis, angiogenesis and restenosis, has not been well studied.

**Brief Summary Paragraph Right (16):**

The present inventors have now found that p27 functions in arteries to control the response to acute injury and cell proliferation. The present inventors provide the first direct demonstration that p27 expression and overexpression is sufficient to produce inhibition of vascular smooth muscle cell growth in vivo. Therefore, the present invention relates to the use of the p27 gene as an anti-proliferative gene to treat vascular proliferative diseases including coronary and peripheral restenosis.

**Detailed Description Paragraph Right (20):**

The amount of p27 to be administered will depend on the size of the patient and the state to which the disease has progressed. By modifying the regulatory elements of the gene using conventional recombinant DNA techniques or by varying the amount of gene titer administered, the amount of p27 expression can be adjusted to the patient's needs. Typically, it is desirable to deliver approximately 50 viral vectors per cell to be treated. With the adenovirus, formulations should generally contain on the order of 10.sup.10 viral infectious units per ml. With retrovirus, slightly different titers may be applicable. See Woo et al., *Enzyme* 1987, 38:207-213. Additional assistance in determining appropriate dosage levels can be found in Kay et al., *Hum. Gene Ther.* 1992, 3:641-647; Liu et al., *Somat. Cell Molec. Genet.* 1992, 18:89-96; and Ledley et al., *Hum. Gene Ther.* 1991, 2:331-358.

**Detailed Description Paragraph Right (21):**

Depending upon the particular formulation that is prepared for the administration of the expression vectors, administration of the compositions of the present invention can be accomplished through a variety of methods. The composition of the present invention are preferably administered by direct injection of the expression vector (or liposome containing the same) into the tissue or by balloon catheter implantation into the blood vessel wall, such as described in U.S. Pat. No. 5,328,470. In a less preferred embodiment, cells from a patient can be collected, transformed with p27 in vitro and replaced in the patient.

**Detailed Description Paragraph Right (26):**

Arterial injury from angioplasty induces a series of proliferative, vasoactive, and inflammatory responses which can lead to restenosis. Although several factors have been defined which stimulate this process in vivo, the role of specific cellular gene products in limiting the response is not well understood. The present inventors have now found that p27 acts to limit the proliferative response to balloon catheter injury. Vascular endothelial and smooth muscle cell growth was arrested through the ability of p27 CKI to inhibit cyclin-dependent kinases and progression through the G.sub.1 phase of the cell cycle. Restenosis is a clinical condition which can be diagnosed and monitored as described in Epstein et al., *JACC* 1994, 23(6): 1278 and Landau et al., *Medical Progress* 1994, 330(14):981.

**Detailed Description Paragraph Right (49):**

L293 cells were transfected with RCMVp16, RCMVp21, RCMVp27, RCMV.beta.-galactosidase or RCMV control plasmid by the calcium phosphate method. The cells were washed in PBS at 48 hours after transfection and pellets were prepared for immunohistochemistry. Antibodies for p27, p21 and p16 were tested on cells transfected with the respective cDNA as well as on cells transfected with the control plasmid. Staining of cells transfected with the respective cDNA was comparable to the transfection efficiency as determined by .beta.-galactosidase expression while cells transfected with the

control plasmid were not stained. Mouse IgG was used as negative control for the monoclonal antibodies and rabbit serum for the polyclonal antibodies. These control primary antibodies did not lead to staining of transfected cells nor arterial specimens. Antibodies were also preabsorbed with lysate from L293 cells transfected with one of the cyclin-dependent kinase inhibitor cDNAs or with the control plasmid. The positive lysates abolished staining of transfected cells and arterial specimens by the respective antibody while the control lysate did not.

**Detailed Description Paragraph Right (50):**

A well characterized arterial specimen from previous studies served as positive control for the smooth muscle .alpha.-actin antibody and human tonsil for the CD68 antibody. Double labeling immunohistochemistry for cyclin-dependent kinase inhibitors plus smooth muscle .beta.-actin or cyclin-dependent kinase inhibitors plus CD68 was performed according to the Vector Laboratories protocol. A red reaction product was chosen for p21 and p27, a blue reaction product for smooth muscle .alpha.-actin and CD68, and the methyl green counter stain was performed as for the single labeling studies.

**Detailed Description Paragraph Right (52):**

Western blot of porcine cell lines from normal and injured arteries were performed. The neointima was fully formed at 21 days. Constitutive p27 expression was detected in quiescent arteries, expression decreased at 1 day, while p27 expression was observed 7 days later increasing at 21 days. The time course and cell type expressing p27 was investigated by immunohistochemistry. Compared to p21 expression, p27 was expressed in smooth muscle cells of normal arterial intimal and media, and in the adventitia. After injury, p27 protein was detected in <1% of these cells and remained low until 7 days when expression was detected in developing neointima. When the neointima was fully formed (21 days), p27 expression was pronounced in the lower regions of the intimal, adjacent to the internal elastic lamina.

**Detailed Description Paragraph Right (53):**

The expression of cyclin-dependent kinase inhibitors after arterial injury was also measured. p27 was expressed at high level in uninjured arteries, at low level at day 7 after injury and at high level again at day 21 after injury. Expression of p21 did not vary much during this time. Expression of p16 could not be detected in uninjured arteries, was present at 4 days after injury and was not present anymore at later time points.

**Detailed Description Paragraph Right (54):**

p27 was expressed at high level in quiescent arteries and from 21 days after injury onwards, while expression markedly declined during the first 14 days after injury. p21 was expressed in quiescent arteries and expression did not vary considerably after injury. p16 could not be detected except at day 1 and 4 after injury. Similar changes in expression were observed for the intimal and for the media.

**Detailed Description Paragraph Right (55):**

In contrast to p21, p27 protein was prominent in all layers of the arteries 60 days later at a time when the repair process had been completed. The expression of p27 was inversely correlated with cell proliferation, previously determined by BrdC incorporation. In contrast, p16 expression was not detected in quiescent or injured arteries by Western analysis or immunohistochemistry.

**Detailed Description Paragraph Right (71):**

Forty specimens of aorta and coronary arteries were obtained from hearts removed from 25 patients (18 men and 7 women, ages 21-67) undergoing heart transplantation. These segments were classified into three groups by classic histological criteria: diffuse intimal hyperplasia, characteristic of aging human arteries without clinical or morphological evidence of atherosclerosis; early atherosclerosis, characterized by some lipid deposition and focal necrosis; and advanced atherosclerosis, with a fibrous cap, necrotic core, lipid deposition, focal necrosis and calcification. Tissues were snap frozen in liquid nitrogen for Western blot analysis and stored at -70.degree. C., or fixed in 10% buffered-formalin for 4 hours, followed by 70% ethanol for 18 hours, and paraffin embedded. Sections (6 mu m thick) were placed onto poly. T. T.

coated slides and immunostaining was performed. Both p27 and p21 were expressed at all stages of atherogenesis while p16 could not be detected in any of the specimens.

Detailed Description Paragraph Right (72):

Atherosclerotic human coronary arteries were double-labeled with anti-p27 or anti-p21 antibodies and a smooth muscle cell marker .alpha.-actin. p27 and p21 expression in the intimal colocalized with smooth muscle cells. Double label immunostaining was performed with p27 and p21 antibodies and a smooth muscle cell marker, .alpha.-actin, using standard techniques. A red reaction product was chosen for p21 and p27, a blue reaction product for smooth muscle .alpha.-actin, and the methyl green counter stain was performed. Smooth muscle .alpha.-actin positive cells (blue) express p21 (red) as well as p27 (red).

Detailed Description Paragraph Right (73):

p27 as well as p21 were present in the intimal, media and adventitia, while p16 could not be detected in these arteries. Expression of p27 and p21 was present in arteries with diffuse intimal hyperplasia as well as in atherosclerotic specimens. Expression of p27 and p21 was associated with .alpha.-actin positive cells and CD 68 positive cells confirming their identity as smooth muscle cells and macrophages. These CKIs were not associated with cells expressing the cell proliferation marker Ki67. These findings indicate that p27 and p21 are expressed in human arteries with diffuse intimal hyperplasia as well as during atherogenesis. In contrast, p16 seems to be expressed at very low level (see Table 1).

Detailed Description Paragraph Right (74):

Expression pattern of p27, p21 and p16 was examined in human coronary arteries with diffuse intimal thickening, beginning atherogenesis and advanced atherogenesis.

Detailed Description Paragraph Right (75):

Transit through G1 of the cell cycle and entry into S phase requires the binding and activation of cyclin/cyclin-dependent kinase (CDK) complexes, predominantly cyclin D-cdk4 and cyclin E-cdk2. The cyclin-dependent kinase inhibitors (CKIs) p27 and p21 inhibit cyclin-cdk activity, resulting in G1/S growth arrest. To determine whatever expression of these CKIs inhibits vsmc proliferation, porcine vsmc were transfected with adenoviral vectors expressing p27, p21 or p16 or a control virus Ad.DELTA.E1. Expression of p27 and p21 resulted in complete inhibition of vsmc proliferation compared to Ad.DELTA.E1 transfected cells ( $p < 0.01$ ) while p16 expression induced a partial inhibition of vsmc growth (63%) compared to controls). Propidium iodide staining and FACS analysis demonstrated G1 arrest. Kinase assays and immunoprecipitation studies demonstrated inhibition of cdk2 activity by p27 and p21 but not p16. To study the effects of CKI expression in vivo. Adenoviral gene transfer of p27 and p16 was performed in balloon injured porcine arteries. Seven days following gene transfer, intimal vsmc proliferation was reduced in p27 arteries compared with p16 and Ad.DELTA.E1 control arteries ( $p < 0.05$ ). This reduction in proliferation was associated with an inhibition of intimal area in p27 arteries ( $0.5 \pm 0.06$  mm<sup>2</sup>) compared with p16 ( $1.13 \pm 0.09$  mm<sup>2</sup>) and Ad.DELTA.E1 control arteries ( $0.98 \pm 0.8$  mm<sup>2</sup>) ( $p < 0.5$ ). Thus, the KIP/CIP CKIs p27 and p21 negatively regulate vsmc proliferation compared to the INK CKI p16. These studies suggest differential roles of KIP/CIP and INK CKIs in regulating G1 arrest in the cell cycle in vsmcs.

Detailed Description Paragraph Table (1):

TABLE 1 Expression of p27 in human coronary arteries Branch LAD LCX RCA Specimens 0 10 16 Intima 7 9 13 Media 7 9 13 Adventitia 8 9 13

Other Reference Publication (3):

Chen et al., "Downregulation of Cyclin-dependent Kinase 2 Activity and Cyclin A Promoter Activity in Vascular Smooth Muscle Cells by p27 .sup.KIP1, an Inhibitor of Neointima Formation in the Rat Carotid Artery," pp. 2334-2341, J. Clin. Invest. 99(10), 1997.

18. Document ID: US 6171790 B1

L14: Entry 18 of 55

File: USPT

Jan 9, 2001

DOCUMENT-IDENTIFIER: US 6171790 B1  
TITLE: Human protease associated proteins

Detailed Description Paragraph Right (51):

In another embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:3, as shown in FIGS. 3A, 3B, and 3C. HPRAP-3 is 239 amino acids in length and has a potential N-glycosylation site at residue N204, and potential phosphorylation sites for casein kinase II at S2, T19, and S65, and for protein kinase C at S46, T74, and S121. As shown in FIGS. 7A and 7B, HPRAP-3 has chemical and structural similarity with the human proteasome subunit, p27 (GI 2055256; SEQ ID NO:11). In particular, HPRAP-3 and p27 share 87% identity. The fragment of SEQ ID NO:7 from about nucleotide 551 to about nucleotide 604 is useful, for example, as a hybridization probe. Northern analysis shows the expression of this sequence in various libraries, at least 51 % of which are immortalized or cancerous and at least 36% of which involve immune response. Of particular note is the expression of HPRAP-3 in cardiovascular, hematopoietic/immune, nervous, and reproductive tissues.

19. Document ID: US 6150395 A

L14: Entry 19 of 55

File: USPT

Nov 21, 2000

DOCUMENT-IDENTIFIER: US 6150395 A  
TITLE: Indole-3-carbinol (I3C) derivatives and methods

Brief Summary Paragraph Right (38):

Our finding that I3C inhibits the protein levels of the CDK6 cell cycle component provides a unique molecular assay to determine the ability of a given I3C derivative to induce a cell cycle arrest of cancer cells. For example, I3C derivatives may be analyzed by western blot to determine the level of CDK6 protein produced in treated or untreated human MCF7 breast cancer cells. In particular, cells are treated with varying concentrations, varying times alone or in the presence of particular sets of anti-estrogens; treatment with I3C may be used as a positive control. The cell extracts are then electrophoretically fractionated in SDS polyacrylamide gels, blotted onto nitrocellular membranes, the blotted proteins probed with CDK6 antibodies and the CDK6 protein visualized by autoradiography. Other G1 acting cell cycle genes may be examined to confirm that a given I3C derivative is acting similarly to I3C itself. For example, the levels of the other cyclin dependent kinases (CDK2 and CDK4), cell cycle activators (cyclin D1, D2, D3 and E) or cell cycle inhibitors (p15, 16, p21 or p27) that function at discrete times within G1 may be assessed in indole treated or untreated MCF7 breast cancer cells. Except for p21 at long times of indole treatment, I3C does not significantly alter the expression of these other cell cycle components.

20. Document ID: US 6140473 A

L14: Entry 20 of 55

File: USPT

Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6140473 A

TITLE: Antibodies specific for MTS2 Polypeptide

Detailed Description Paragraph Right (191):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDKs. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDKs are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

21. Document ID: US 6090578 A

L14: Entry 21 of 55

File: USPT

Jul

18, 2000

DOCUMENT-IDENTIFIER: US 6090578 A

TITLE: MTS1 gene

Detailed Description Paragraph Right (206):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b;

22. Document ID: US 6068982 A

L14: Entry 22 of 55

File: USPT

May 30, 2000

DOCUMENT-IDENTIFIER: US 6068982 A

TITLE: Ubiquitin conjugating enzymes

Detailed Description Paragraph Right (167):

The subject E2 inhibitors can also be used in the treatment of hyperproliferative vascular disorders, e.g. smooth muscle hyperplasia (such as atherosclerosis) or restenosis, as well as other disorders characterized by fibrosis, e.g. rheumatoid arthritis, insulin dependent diabetes mellitus, glomerulonephritis, cirrhosis, and scleroderma, particularly proliferative disorders in which loss of TGF- $\beta$ . autocrine or paracrine signaling is implicated. For example, restenosis continues to limit the efficacy of coronary angioplasty despite various mechanical and pharmaceutical interventions that have been employed. An important mechanism involved in normal control of intimal proliferation of smooth muscle cells appears to be the induction of autocrine and paracrine TGF- $\beta$ . inhibitory loops in the smooth muscle cells (Scott-Burden et al. (1994) Tex Heart Inst J 21:91-97; Grainger et al. (1993) Cardiovasc Res 27:2238-2247; and Grainger et al. (1993) Biochem J 294:109-112). Loss of sensitivity to TGF- $\beta$ ., or alternatively, the overriding of this inhibitory stimulus such as by PDGF autostimulation, can be a contributory factor to abnormal smooth muscle proliferation in restenosis. It may therefore be possible to treat or prevent restenosis by the use of agents which inhibit ubiquitination of p27, thereby causing its accumulation.

23. Document ID: US 6060301 A

L14: Entry 23 of 55

File: USPT

May 9, 2000

DOCUMENT-IDENTIFIER: US 6060301 A  
TITLE: Vector containing MTS1E1.beta. gene

Detailed Description Paragraph Right (219):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDK's. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDK's are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

24. Document ID: US 6043254 A

L14: Entry 24 of 55

File: USPT

Mar 28, 2000

DOCUMENT-IDENTIFIER: US 6043254 A  
TITLE: Indolinones having kinase-inhibiting activity

Brief Summary Paragraph Right (5):

Another major mechanism of CDK regulation involves a family of different proteins, so-called cycline-dependent kinase inhibitors (CKIs) which bind and inhibit cycline/CDK complexes (cf. G. Peters in Nature 371, 204-205 (1994)). The chief (mammalian) CKIs fall into two categories: (1): p21 (CIP1/WAF1/CAP20/SD1), p27 (KIP1) and p57 (KIP2) are related proteins with a preference for cycline/CDK2 and cycline/CDK4 complexes; (2) p16.sup.INK4, p15.sup.INK4B, p18.sup.INK4C and p19.sup.INK4D are closely related CKIs with a specificity for CDK4 and/or CDK6. p21 primarily regulates transcription. p21 transcription is induced by the tumour-suppressor gene p53, a transcriptional regulator which mediates the stopping of the cell cycle after DNA damage or in

senescence. Basal concentrations of p21 may possibly constitute a threshold which has to be crossed before complexes can become active. Transcriptional control may possibly also be important for p15.sup.INK4B, the expression of which is greatly increased when treated with the negative growth factor TGF.beta.. An additional effect of TGF.beta. is obviously the release of p27, which is established in a heat-sensitive compartment. p27 is probably also involved in the effects of positive growth factors. For example, interleukin-2 stimulation appears to induce a fall in the concentration of p27 and as a result the proliferation of T-cells.

25. Document ID: US 6037462 A

L14: Entry 25 of 55

File: USPT

Mar 14, 2000

DOCUMENT-IDENTIFIER: US 6037462 A  
TITLE: MTS1 gene mutations

Detailed Description Paragraph Right (187):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDK's. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDK's are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

26. Document ID: US 6025480 A

L14: Entry 26 of 55

File: USPT

Feb 15, 2000

DOCUMENT-IDENTIFIER: US 6025480 A

TITLE: Isolated nucleic acid molecules encoding P57KIP2

**Brief Summary Paragraph Right (6):**

Despite their recent identification, it is clear that the CDIs play a pivotal role in cell cycle control. Their nature as putative tumor suppressor genes has important implications for diagnosis and treatment of hyperproliferative disorders. Furthermore, the known CDIs are notorious for their structural and functional diversity, suggesting that they may be but the first identified examples of a larger group whose components have highly specialized structure and function. Given this possibility, applicants searched for additional members of the p21/p27 family. Applicants have isolated a new member of the p21.sup.CIP1 /p27.sup.KIP1 CDI family and named it p57.sup.KIP2 to denote its apparent molecular mass and higher similarity to p27.sup.KIP1. Three distinct p57 cDNAs were cloned that differ at the start of their open reading frames and correspond to messages generated by the use of distinct splice acceptor sites. p57 is distinguished from p21 and p27 by its unique domain structure. Four distinct domains follow the heterogeneous N-terminal region and include, in order, a p21/p27-related CDK inhibitory domain, a proline-rich (28% proline) domain, an acidic (36% glutamic or aspartic acid) domain, and a C-terminal nuclear targeting domain that contains a putative CDK phosphorylation site and has sequence similarity to p27 but not to p21. Most of the acidic domain consists of a novel, tandemly repeated four-amino acid motif. p57 is a potent inhibitor of G1 and S phase CDKs (cyclin E-cdk2, cyclin D2-cdk4 and cyclin A-cdk2) and, to lesser extent, of the mitotic cyclin B-Cdc2. In mammalian cells, p57 localizes to the nucleus, associates with G1 CDK components, and its overexpression causes a complete cell cycle arrest in G1 phase. In contrast to the widespread expression of p21 and p27 in human tissues, p57 is expressed in a tissue-specific manner, as a 1.5 kb species in placenta and at lower levels in various other tissues, and a 7 kb mRNA species observed in skeletal muscle and heart. The expression pattern and unique domain structure of p57 suggest that this CDI may play a specialized role in cell cycle control.

**Detailed Description Paragraph Right (108):**

Northern blot assays with a mouse p57 cDNA probe used at high stringency showed the presence of hybridizing RNA species of 1.5 kb and 7 kb in a limited subset of human tissues (FIG. 9). This is in contrast to the presence of a single p27 mRNA in all these tissues as determined by probing of the same blot with a p27 probe (FIG. 9; Polyak et al. 1994b). The 1.5 kb p57 mRNA species was present at relatively high levels in placenta, at low levels in skeletal muscle, heart, kidney and pancreas, was detectable in brain only after prolonged autoradiographic exposure of the blot, and was not detectable in lung or liver. Among the tissues tested, the 7 kb species was detectable only in skeletal muscle and heart (FIG. 9), and in two human rhabdomyosarcoma cell lines (data not shown). The relationship between these two mRNA species and the basis for their marked size difference remain to be determined.

**Detailed Description Paragraph Right (117):**

The expression pattern of p57 mRNA in various adult human tissues suggests that its distribution is more restricted than that of p21 and p27, both of which are expressed in most tissues examined (Harper et al. 1993; Polyak et al. 1994b). Two human mRNA species of 1.5 kb and 7 kb, respectively, hybridize with the mouse p57 probe under relatively high stringency conditions. The basis for the size difference between these two messages remains to be determined, but may result from differential processing of the p57 transcript or from the existence of different p57-related genes. The 7 kb mRNA is detectable only in skeletal muscle and

heart among the tissues that applicants tested, and in human rhabdomyosarcoma cells. The 1.5 kb species is present in placenta and at low levels in muscle, heart, brain, kidney and pancreas, and was not detected in lung or liver. Some of these tissues are highly heterogeneous in cellular composition, and their low p57 mRNA levels may reflect expression in only certain cell types.

27. Document ID: US 6001868 A

L14: Entry 27 of 55

File: USPT

Dec 14, 1999

DOCUMENT-IDENTIFIER: US 6001868 A

TITLE: Indole-3-carbinol (I3C) derivatives and methods

**Brief Summary Paragraph Right (33):**

Our finding that I3C inhibits the protein levels of the CDK6 cell cycle component provides a unique molecular assay to determine the ability of a given I3C derivative to induce a cell cycle arrest of cancer cells. For example, I3C derivatives may be analyzed by western blot to determine the level of CDK6 protein produced in treated or untreated human MCF7 breast cancer cells. In particular, cells are treated with varying concentrations, varying times alone or in the presence of particular sets of anti-estrogens; treatment with I3C may be used as a positive control. The cell extracts are then electrophoretically fractionated in SDS polyacrylamide gels, blotted onto nitrocellulose membranes, the blotted proteins probed with CDK6 antibodies and the CDK6 protein visualized by autoradiography. Other G1 acting cell cycle genes may be examined to confirm that a given I3C derivative is acting similarly to I3C itself. For example, the levels of the other cyclin dependent kinases (CDK2 and CDK4), cell cycle activators (cyclin D1, D2, D3 and E) or cell cycle inhibitors (p15, 16, p21 or p27) that function at discrete times within G1 may be assessed in indole treated or untreated MCF7 breast cancer cells. Except for p21 at long times of indole treatment, I3C does not significantly alter the expression of these other cell cycle components.

28. Document ID: US 5994095 A

L14: Entry 28 of 55

File: USPT

Nov 30, 1999

DOCUMENT-IDENTIFIER: US 5994095 A

TITLE: MTS2 gene

**Detailed Description Paragraph Right (186):**

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus in that they regulate by phosphorylation the activity of other proteins involved in cell cycle control.

that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDKs. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDKs are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

29. Document ID: US 5989815 A

L14: Entry 29 of 55

File: USPT

Nov 23, 1999

DOCUMENT-IDENTIFIER: US 5989815 A

TITLE: Methods for detecting predisposition to cancer at the MTS gene

Detailed Description Paragraph Right (189):

In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDKs. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk (Xiong et

al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDKs are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

30. Document ID: US 5968761 A

L14: Entry 30 of 55

File: USPT

Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968761 A

TITLE: Ubiquitin conjugating enzymes

Detailed Description Paragraph Right (159):

The subject E2 inhibitors can also be used in the treatment of hyperproliferative vascular disorders, e.g. smooth muscle hyperplasia (such as atherosclerosis) or restenosis, as well as other disorders characterized by fibrosis, e.g. rheumatoid arthritis, insulin dependent diabetes mellitus, glomerulonephritis, cirrhosis, and scleroderma, particularly proliferative disorders in which loss of TGF- $\beta$ . autocrine or paracrine signaling is implicated. For example, restenosis continues to limit the efficacy of coronary angioplasty despite various mechanical and pharmaceutical interventions that have been employed. An important mechanism involved in normal control of intimal proliferation of smooth muscle cells appears to be the induction of autocrine and paracrine TGF- $\beta$ . inhibitory loops in the smooth muscle cells (Scott-Burden et al. (1994) Tex Heart Inst J 21:91-97; Graiger et al. (1993) Cardiovasc Res 27:2238-2247; and Grainger et al. (1993) Biochem J 294:109-112). Loss of sensitivity to TGF- $\beta$ ., or alternatively, the overriding of this inhibitory stimulus such as by PDGF autostimulation, can be a contributory factor to abnormal smooth muscle proliferation in restenosis. It may therefore be possible to treat or prevent restenosis by the use of agents which inhibit ubiquitination of p27, thereby causing its accumulation.

31. Document ID: US 5961976 A

L14: Entry 31 of 55

File: USPT

Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5961976 A

TITLE: Antibodies against a host cell antigen complex for pre- and post-exposure protection from infection by HIV

Detailed Description Paragraph Right (180):

The experiment shown in Table 14 compares the neutralization activities of B4 (group 5 of Table 3, Example 4) and polyclonal anti-N-terminal V3 MN (group 6 of Table 3) against various isolates of HIV-2, SIV, and recombinant SHIV. Isolate designations are as shown on the table. Neutralization determinations on HIV-2.sub.287 were by Infectivity Reduction Assay (IRA) (White-Scharf et al., Virology, 1993, 192:197-206). IRA results are expressed as infectious units >95% inactivated by 10 .mu.g/mL of antibody. Neutralization activities on HIV-2.sub.ROD were determined by MT-2 assay as described in Example 1. Neutralization assays on SIV.sub.251, SIV.sub.239, and HIV-1/SIV recombinants SHIV.sub.IIB, and SHIV.sub.89.6 were determined by p27 Antigen Neutralization Assay (Gardner et al., AIDS Res Hum Retroviruses, 1995, 11:843) of the infected PBMC cultures to the 50% endpoint, except for one set of neutralization determinations for B4 on PBMC-grown SIV.sub.251 which were carried out to an 80% endpoint. The 50% and 80% endpoints are the fractions of detectable p27 in antibody-treated cultures compared to untreated cultures.

32. Document ID: US 5958769 A

L14: Entry 32 of 55

File: USPT

Sep 28, 1999

DOCUMENT-IDENTIFIER: US 5958769 A

TITLE: Compositions and methods for mediating cell cycle progression

Brief Summary Paragraph Right (9):

In other embodiments the invention provides methods for increasing the proportion of dividing cells in a vertebrate cell population. A population of cells is exposed to a p27 inhibitor in an amount sufficient to increase the proportion of dividing cells to non-dividing cells relative to said proportion in a population of untreated cells. Such cell population can be a substantially non-dividing or terminally differentiated primary cell population, including, e.g., fibroblasts, osteoblasts, myeloblasts, neurons or epithelial cells. Isolated hematopoietic progenitor cells are particularly useful in the present methods. The cells can be exposed to the inhibitor either in vitro or in vivo. When performed in vitro, the method can further comprise the step of administering the exposed cells to a host, particularly when the exposed cells have been transduced to express a desired gene. Thus, the method provides for increasing the efficiency of transducing a vertebrate cell population with a viral vector encoding a gene product of interest. The target cells, e.g., mammalian hematopoietic progenitor cells, are exposed to a p27 inhibitor in an amount sufficient to increase the percentage of dividing cells, and contacting the treated cells to a viral vector encoding the gene product of interest.

Detailed Description Paragraph Right (14):

A sequence comprising or encoding an oligonucleotide p27 inhibitor, e.g., triplex forming oligonucleotides, antisense oligonucleotide, ribozyme, etc., or a combination of such inhibitors targeted to different portions of the p27 DNA or corresponding RNA can be delivered in a wide variety of ways to targeted cells to facilitate progression of the cell cycle. The oligonucleotides can be administered as synthetic oligonucleotides or expressed from an expression vector. The oligonucleotide can be administered ex vivo, i.e., contacted with target cells that have been removed from an individual or other cell source, treated and returned, or the oligonucleotide molecule can be administered in vivo. When administered ex vivo typically the target cells are exposed to mitogens, e.g., serum mitogens (SCF, IL-3, EPO, TPO, etc.) or the like depending on particular cell population

Detailed Description Paragraph Right (21):

Cells which are exposed to a p27 inhibitor in an amount and for a time sufficient to inhibit exit from the cell cycle can be treated by a variety of substances that target dividing cells. In one embodiment, for example, a cell population in which the proportion of dividing cells has been increased by a p27 inhibitor are more efficiently transduced or transfected with a nucleotide sequence encoding a gene product of interest. Thus, the methods described herein increase the efficiency of gene therapy techniques. For example, target cells treated with a p27 inhibitor are transduced with at least one gene encoding an expression product of interest, typically an RNA or protein molecule. The encoded RNA or protein is one which confers a benefit to the cell population or host being treated, either directly or indirectly. The gene may encode a secreted or non-secreted protein, or an active portion thereof. The selection of a suitable gene for the condition being treated will depend on the condition being treated or prevented and other factors apparent to those skilled in the art. By "gene" is meant DNA that encodes a desired product, such as, for example, a cytokine, a clotting factor, a hormone, an enzyme, a transport protein, a regulatory protein, a structural protein, a receptor, an antigen, ribozyme, antisense molecule, etc. Representative examples of genes for introducing into humans are those encoding human erythropoietin (described in U.S. Pat. No. 4,703,008), human G-CSF, human GM-CSF (Anderson et al., Proc. Natl. Acad. Sci. USA 82:6250 (1985)), plasminogen activator, urokinase, insulin (e.g., human insulin as described in U.S. Pat. No. 4,652,525 or proinsulin described in U.S. Pat. No. 4,431,740), interleukins (e.g., interleukin-1, interleukin-2 [described in U.S. Pat. No. 4,738,927], interleukin-3 [described in EP Publ. 275,598 and 282,185], interleukin-4, interleukin-7 [U.S. Pat. No. 4,965,195], etc.), interferons, Factor VIII, Factor IX, von Willebrand Factor, ADA, human growth hormone (described in U.S. Pat. No. 4,342,832), etc., analogs and fusions thereof (e.g., fusions of GM-CSF and IL-3 [U.S. Pat. No. 5,108,910]). Each of the foregoing patents and publications is expressly incorporated herein by reference.

Detailed Description Paragraph Right (26):

The present invention is particularly preferred for increasing the proportion of dividing cells in a population of hematopoietic precursor cells, especially those of human and other mammals, either ex vivo or in vivo. In an ex vivo method, hematopoietic precursor cells are separated from a blood product, such as bone marrow, peripheral blood, or umbilical cord blood of a donor, fetal peripheral blood and other sources. Such separation may be performed, for example, by immunoselection on the basis of their expression of an antigen, such as the CD34 antigen which is present on substantially all human hematopoietic precursor cells, but is substantially absent from more mature hematopoietic cells. The separated hematopoietic precursor cells may be stored frozen and thawed at a later date for inoculation into a suitable vessel containing a culture medium comprising a nutritive medium. Alternatively, the separated cells may be inoculated directly into culture without first freezing. In both cases the resultant cell suspension is cultured with a p27 inhibitor as described herein under conditions and for a time sufficient to increase the proportion of dividing hematopoietic precursor cells relative to the proportion of such cells present initially in the blood product. The cells may then be treated with vector capable of expressing the gene product of interest. The cells may then be infused or implanted into a host or stored frozen for infusion at a later date.

Detailed Description Paragraph Right (33):

The relationship between p27 expression and cell proliferation was studied by testing the relative abilities of specific serum mitogens to both downregulate p27 and induce cell proliferation. Flow cytometry analysis was performed on both the asynchronously proliferating Balb/c-3T3 cells (Hi serum) and subconfluent Balb/c-3T3 cells that had been serum-starved for 24 hours (Low serum) in the presence of either individual growth factors (PDGF, IGF-I or EGF) or all three growth factors (PIE) (see Table). p27 immunoblots were performed on cell extracts (10 ug) from cells treated with growth factors. Only PDGF was able to prevent G1 arrest, and only PDGF prevented the induction of p27. Balb/c-3T3 fibroblasts grown at high density have more complex mitogen requirements than when grown subconfluently; no single mitogen is able to cause proliferation of cells at high density. U.S. A.

PDGF initially stimulates the density arrested, quiescent cells to become "competent" to respond to "progression" factors, IGF-1 and EGF (Pledger et al., Proc. Natl. Acad. Sci. USA 74:4481 (1977); Leof et al., Exp. Cell Res. 147:202 (1983)). Therefore, under these conditions passage through the restriction point does not occur until cells have been exposed to all three mitogens.

Detailed Description Paragraph Right (41):

Cell extracts from the serum-starved (24 hours in low serum medium containing 0.1% serum) Balb/c-3T3 fibroblasts transfected with the p27 antisense or mismatch control oligonucleotides were analyzed by immunoblotting with anti-p27 antiserum. The immunoblots showed that expression of p27 protein was substantially decreased in the antisense treated cells (FIG. 1A) while the mismatch oligonucleotide had no effect on accumulation of p27 following serum withdrawal. While the results were shown for one antisense and one control oligonucleotide, identical results were obtained with the other antisense and control oligonucleotides.

Detailed Description Paragraph Right (46):

In sum, these results show that cells treated with p27 antisense oligonucleotides failed to induce p27 protein in response to mitogen depletion, and were unable to exit the cell cycle. Although the duration of the effect for this antisense preparation was limited, cells treated with p27 antisense expressed low levels of p27 protein and continued to proliferate for at least 48 hours without serum mitogens.

Detailed Description Paragraph Right (52):

A p27 wobble plasmid was then used to determine whether expression of p27 protein in the antisense treated cells renewed their responsiveness to mitogen depletion. These experiments were designed to study the physiological effects of p27 expression, and therefore used a wobble plasmid encoding fully wild type p27, rather than the electrophoretic variant described above. Balb/c-3T3 cells were lipofected with mismatch or p27 antisense oligonucleotides, and then microinjected with a both plasmid encoding .beta.-galactosidase (to mark the injected cells) and with the p27 wobble plasmid. Microinjection, immunofluorescence staining, and fluorescence microscopy were carried out as described in Fisher et al., Nuc. Acid Res. 21:3857 (1993); Hanvey et al., Science 258: 1481 (1992); Wagner et al., Science 260:1510 (1993); Moulds et al., Biochem. 34:5044 (1995), each of which is incorporated herein by reference. Cells were rinsed once in serum-free medium and were then serum-starved in low serum medium containing 0.1% serum for 24 hours. As described above, the cells were pulse-labeled with BrdU for three hours followed by immunostaining for both BrdU and .beta.-galactosidase. For costaining of .beta.-galactosidase and BrdU, the cells were fixed, and then first incubated with a polyclonal anti-.beta. galactosidase antibody (5'3' Inc. Boulder, Co.) for 60 minutes, followed by incubation with a fluorescein-conjugated goat anti-rabbit IgG (Jackson Immunoresearch Laboratories, West Grove, Pa.) for 30 minutes. The cells were then incubated with a fluorescein-conjugated rabbit anti-goat IgG antibody for 30 minutes. At the end of this procedure, the slides were fixed again with 3.7% formaldehyde for 10 minutes followed by incubation in acetone for 1 minute. The cells were rehydrated with TBS followed by a 10 minute treatment with 4N HCl and a final wash with TBS. To visualize the BrdU staining, the cells were incubated for 1 hour with a monoclonal anti-BrdU antibody (Boehringer Mannheim, Germany), followed by a 30 minute incubation with a rhodamine-conjugated donkey anti-mouse antibody (Jackson Immunoresearch Laboratories, West Grove, Pa.). The percentage of cells in S phase measured by pulse labeling with BrdU which was carried out as described above. The percent of .beta.-galactosidase positive cells that incorporated BrdU was determined and expressed as the percent of cells in S phase as compared to the total number of cells staining positive for .beta.-galactosidase expression. Lipofection of cells with p27 antisense oligonucleotides markedly decreased the percentage of cells that withdrew from the cell cycle following mitogen depletion, and this was reversed by microinjection with the p27 wobble plasmid (FIG. 2B).

Detailed Description Paragraph Right (53):

These results showed that the inability of p27 antisense treated cells to exit the cell cycle after mitogen depletion is specifically caused by the loss of p27 expression.

33. Document ID: US 5912176 A

L14: Entry 33 of 55

File: USPT

Jun 15, 1999

DOCUMENT-IDENTIFIER: US 5912176 A

TITLE: Antibodies against a host cell antigen complex for pre and post exposure protection from infection by HIV

Detailed Description Paragraph Right (188):

The experiment shown in Table 14 compares the neutralization activities of B4 (group 5 of Table 3, Example 4) and polyclonal anti-N-terminal V3 MN (group 6 of Table 3) against various isolates of HIV-2, SIV, and recombinant SHIV. Isolate designations are as shown on the table. Neutralization determinations on HIV-2.sub.287 were by Infectivity Reduction Assay (IRA) (White-Scharf et al., Virology, 1993, 192:197-206). IRA results are expressed as infectious units >95% inactivated by 10 .mu.g/mL of antibody. Neutralization activities on HIV-2.sub.ROD were determined by MT-2 assay as described in Example 1. Neutralization assays on SIV.sub.251, SIV.sub.239, and HIV-1/SIV recombinants SHIV.sub.IIIB, and SHIV.sub.89.6 were determined by p27 Antigen Neutralization Assay (Gardner et al., AIDS Res Hum Retroviruses, 1995, 11:843) of the infected PBMC cultures to the 50% endpoint, except for one set of neutralization determinations for B4 on PBMC-grown SIV.sub.251 which were carried out to an 80% endpoint. The 50% and 80% endpoints are the fractions of detectable p27 in antibody-treated cultures compared to untreated cultures.

34. Document ID: US 5872429 A

L14: Entry 34 of 55

File: USPT

Feb 16, 1999

DOCUMENT-IDENTIFIER: US 5872429 A

TITLE: Coded communication system and method for controlling an electric lamp

Detailed Description Paragraph Right (86):

The heart of the interface circuit is the microcontroller IC2 (for example, a Z86C04 from Zilog, Inc.) which converts the dimming control signals to a corresponding PWM (Pulse Width Modulation) output. The microcontroller IC2 has three inputs P31, P32 and P33 which accept the coded, step, and phase angle dimming signals, respectively. The PWM output (dim) signal is formed on terminal P27 and is converted to a DC signal for input to the half-bridge driver at the 'dim' input of IC-U4 to adjust the power to the lamp.

35. Document ID: US 5843756 A

L14: Entry 35 of 55

File: USPT

Dec 1, 1998

DOCUMENT-IDENTIFIER: US 5843756 A  
TITLE: Mouse MTS1 gene

Detailed Description Paragraph Right (194):  
In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the Cdk's. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or Cdk4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and Cdk's are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

36. Document ID: US 5821072 A

L14: Entry 36 of 55

File: USPT

Oct 13, 1998

DOCUMENT-IDENTIFIER: US 5821072 A  
TITLE: Combinations of PKC inhibitors and therapeutic agents for treating cancers

Detailed Description Paragraph Right (94):  
(iii) To examine in vitro cdk2 and to identify other related cell cycle dependent proteins associated with the induction of

apoptosis and the inhibition of PKC: The basis for the increase in cdk2 activity by safingol and MMC in combination remains unknown. It may be related to a decrease in the expression of a cdk2 inhibitor (i.e. p21) or it may be related to a modification of a phosphorylated site on cdk2 which results in its activation. A further understanding of this process may lead to new surrogate markers of activity. In order to examine this further applicants plan to examine: 1) protein expression of p21 and p27 with immunoblotting using an enhanced chemiluminescence system using specific antibodies (Santa Cruz Biotechnology, Inc. Santa Cruz, Calif.); 2) differences in protein phosphorylation of cdk2 with [<sup>32</sup>P]orthophosphate cell labelling, as previously described, using a cdk2 specific antibody suitable for immunoprecipitating (36); and 3) correlative studies of cdk2 activity as measured by the histone H1 kinase assays (38). Control cells will be treated in the same way as described above except that standard media without drug will be used for all incubations.

37. Document ID: US 5801236 A

L14: Entry 37 of 55

File: USPT

Sep 1, 1998

DOCUMENT-IDENTIFIER: US 5801236 A  
TITLE: Probes for MTS1 gene and polynucleotides encoding mutant MTS1 genes

Detailed Description Paragraph Right (187):  
In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p13, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDK's. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay. (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDK's are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division

38. Document ID: US 5753674 A

L14: Entry 38 of 55

File: USPT

May 19, 1998

DOCUMENT-IDENTIFIER: US 5753674 A

TITLE: Adenosine diphosphoribose polymerase binding nitroso aromatic compounds useful as retroviral inactivating agents, anti-retroviral agents, anti-retroviral agents and anti-tumor agents

Drawing Description Paragraph Right (16):  
FIGS. 14A-B. The effect of NOBA on SIV.sub.mac 239 replication (FIG. 14A) and CEM x174 cell viability (FIG. 14B). Each bar expresses the mean of 3 independent tests, which do not differ  $\pm 10\%$  (not shown). In FIG. 14A, ordinate=p27 antigen assay (ELISA) performed on day 10; abscissa=concentration of NOBA or DMSO. In FIG. 14B, cell viability test determined on day 10 by the tetrazolium assay first line bars=virus infected cells (SIV) in presence of NOBA; second line bars (controls)=uninfected cells treated with NOBA.

39. Document ID: US 5739027 A

L14: Entry 39 of 55

File: USPT

Apr 14, 1998

DOCUMENT-IDENTIFIER: US 5739027 A

TITLE: MTS1E1.beta. gene

Detailed Description Paragraph Right (186):  
In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the Cdk's. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction

with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and Cdk's are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p18, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

40. Document ID: US 5691605 A

L14: Entry 40 of 55

File: USPT

Nov 25, 1997

DOCUMENT-IDENTIFIER: US 5691605 A

TITLE: Electronic ballast with interface circuitry for multiple dimming inputs

Detailed Description Paragraph Right (74):  
The heart of the interface circuit is the microcontroller IC2 (for example, a Z86C04 from Zilog, Inc.) which converts the dimming control signals to a corresponding PWM (Pulse Width Modulation) output. The microcontroller IC2 has three inputs P31, P32 and P33 which accept the coded, step, and phase angle dimming signals, respectively. The PWM output (dim) signal is formed on terminal P27 and is converted to a DC signal for input to the half-bridge driver at the 'dim' input of IC-U4 to adjust the power to the lamp.

41. Document ID: US 5688665 A

L14: Entry 41 of 55

File: USPT

Nov 18, 1997

DOCUMENT-IDENTIFIER: US 5688665 A

TITLE: Isolated nucleic acid molecules encoding the p27 KIP-1 protein

Detailed Description Paragraph Right (57):  
The subject invention further provides a method for quantitatively determining the level of expression of p27 in a cell population, and a method for determining whether an agent is capable of increasing or decreasing the level of expression of p27 in a cell population. The method for determining whether an agent is capable of increasing or decreasing the level of expression of p27 in a cell population comprises the steps of (a) preparing cell extracts from control and agent-treated cell populations, (b) isolating p27 from the cell extracts (e.g., by affinity chromatography on, and elution from, a cyclin E-Cdk2 complex solid phase affinity adsorbant), (c) quantifying (e.g., in parallel) the amount of p27 inhibitor activity in the control and agent treated

cell extracts using a cyclin E-Cdk2 kinase assay (e.g., histone H1 assay described infra). Agents that induce increased p27 expression may be identified by their ability to increase the amount of p27 inhibitor activity in the treated cell extract in a manner that is dependant on transcription, i.e., the increase in p27 inhibitor activity is prevented when cells are also treated with an inhibitor of transcription (e.g., actinomycin D). In a similar manner, agents that decrease expression of p27 may be identified by their ability to decrease the amount of p27 inhibitor activity in the treated cell extract in a manner that is dependent upon transcription.

tetrazolium assay first line bars=virus infected cells (SIV) in presence of NOBA; second line bars (controls)=uninfected cells treated with NOBA.

44. Document ID: US 5624819 A

L14: Entry 44 of 55

File: USPT

Apr 29, 1997

42. Document ID: US 5672508 A

L14: Entry 42 of 55

File: USPT

Sep 30, 1997

DOCUMENT-IDENTIFIER: US 5672508 A

TITLE: Inhibitors of cell-cycle progression, and uses related thereto

Detailed Description Paragraph Right (83):  
The subject method can also be used to treat retinoblastomas in which the retinoblastoma gene (RB) is not itself impaired, e.g. the effective impairment of the RB checkpoint is the result of a failure to control CDK4 phosphorylation of RB. Thus, one of the subject fusion proteins can be expressed in a retinoblastoma cell, thereby causing inhibition of CDK4 activation and down-regulating RB phosphorylation. To illustrate, a recombinant retrovirus can be constructed to facilitate expression of a fusion protein including an INK4 protein, e.g., derived from p16 or p15, and a CIP protein, e.g., derived from p21, p27 or p57. Infectivity of retinoblastoma cells can be enhanced by derivatizing the env protein with antibodies specific for retinoblastoma cells, e.g. antibodies to retinal S-antigen (Doroso et al. (1985) Invest Ophthalmol Vis Sci 26:560-572; see also Liao et al. (1981) Eur J Immunol 11:450-454; and U.S. Pat. No. 4,444,744).

DOCUMENT-IDENTIFIER: US 5624819 A

TITLE: Germline mutations in the MTS gene

Detailed Description Paragraph Right (186):  
In all eukaryotic cells, cell division requires passage through two critical decision points: the G1 to S transition, where DNA synthesis commences, and the G2 to M transition, where mitosis begins. In mammals, the machinery that controls cell division has multiple components, many of which are related (for review see Sherr, 1993). The Cdk's may be at the heart of the control apparatus, in that they regulate by phosphorylation a number of key substrates that in turn trigger the transition from G1 to S and from G2 to M. The G1 to S transition is perhaps the more critical decision point, as it occurs first in the cell cycle. So far, four types of Cdk have been defined (Cdk2-5) that may participate in G1 to S control, as well as a set of positive regulators of these Cdk's (cyclins C, D1-3, E). Recently several negative regulators have also been identified, including p16, p15, p18, p20, p21, and p27 (Xiong et al., 1993; Serrano et al., 1993; Gu et al., 1993; El-Diery et al., 1993; Harper et al., 1993; Hannon and Beach, 1994; Polyak et al., 1994b; Toyoshima and Hunter, 1994; Guan et al., 1995). These negative regulators appear to act by inhibiting the kinase activity of the CDKs. Some of the cell cycle regulators are involved in human cancers (for review, see Hunter and Pines, 1994). p20 inhibits Cdk2 and possibly other Cdk's while p16 (also called MTS1, CDKN2, or INK4a) inhibits Cdk4 but apparently does not inhibit Cdk2 in an in vitro assay (Serrano et al., 1993). Based on in vitro studies and on its interaction with p53, p21 has been proposed as a general inhibitor of all Cdk's (Xiong et al., 1993). Thus, in vitro, p16 appears more specific than p21. Each of these inhibitors is expected to antagonize entry into S phase. Also, cyclin D1 or CDK4 is overexpressed in some breast carcinomas and the p16 gene is mutated or deleted in a large number of cell lines and primary tumors (Buckley et al., 1993; Caldas et al., 1994; Kamb et al., 1994b; Mori et al., 1994; Tam et al., 1994a). These results suggest that certain cyclins and CDKs are protooncogenes and that P16 (MTS1) is a tumor suppressor gene. The biochemical behavior of p15, p16, p21 and p27 indicate that they too may be tumor suppressors, but detailed mutational analysis of their genes in tumors or cell lines has not been reported. The results presented here provide evidence that MTS1 functions in vivo as an inhibitor of cell division.

43. Document ID: US 5652260 A

L14: Entry 43 of 55

File: USPT

29, 1997

Jul

DOCUMENT-IDENTIFIER: US 5652260 A

TITLE: Adenosine diphosphoribose polymerase binding nitroso aromatic compound useful as retroviral inactivating agents, anti-retroviral agents and anti-tumor agents

Drawing Description Paragraph Right (16):  
FIGS. 14A-B. The effect of NOBA on SIV.sub.mac 239 replication (FIG. 14A) and CEM x174 cell viability (FIG. 14B). Each bar expresses the means of 3 independent tests, which do not differ  $\pm 10\%$  (not shown). In FIG. 14A, ordinate=p27 antigen assay (ELISA) performed on day 10; abscissa=concentration of NOBA or DMSO. In FIG. 14B, cell viability test determined on day 10 by the

45. Document ID: US 5601819 A

L14: Entry 45 of 55

File: USPT

Feb 11, 1997

DOCUMENT-IDENTIFIER: US 5601819 A

TITLE: Bispecific antibodies for selective immune regulation and for selective immune cell binding

Detailed Description Paragraph Right (40):

Similarly, the optimum concentration range for ADCC can be determined by the technique of Kipps et al., J. Exp. Med. 161:1-17 (1985), except that the target cells will be those that express both antigens recognized by the bispecific monoclonal antibody. Antibody will be added in increasing concentrations. Effector cells used are the U937 cell line treated with 1000U/ml of .sub..gamma. -interferon or adherent cells from peripheral blood.

46. Document ID: US 4701750 A

L14: Entry 46 of 55

File: USPT

Oct 20, 1987

DOCUMENT-IDENTIFIER: US 4701750 A

TITLE: Motorcycle sound simulator for non-motorized vehicle

Detailed Description Paragraph Right (2):

Turning to FIG. 2, namely the schematic diagram, there can be seen the essential features of the electronic circuitry within unit 12. At the heart of the system is a microprocessor 30 which, in the preferred embodiment, is an Intel 8048. The data input pins DB-0 to DB-7 are used only at initialization and it can be seen that the sample time frame of 192 units (of 350 microseconds each) is hardwired thereon. This value is the number of timer interrupts in the wheel sensor sample, as will be explained hereinafter. Pins P20-P27 are supplementary data inputs and are not presently used in the preferred embodiment.

47. Document ID: US 4430639 A

L14: Entry 47 of 55

File: USPT

Feb 7, 1984

DOCUMENT-IDENTIFIER: US 4430639 A

TITLE: Visual message intercommunication unit and system

Detailed Description Paragraph Right (53):

At the heart of each unit is a central processing unit (CPU) 52 which is an eight-bit, type 8039 microprocessor, manufactured by Intel Corporation, Santa Clara, CA. CPU 52 includes an internal random access memory (RAM), as indicated, for storing composed and received messages and for holding such messages for display. CPU 52 is connected to keyboard 20 by a bus which has five leads, as indicated by the designation "(5)". Terminals P10 to P17, P24 to P27, and T1 of CPU 52 are connected to keyboard 20.

48. Document ID: US 4147869 A

L14: Entry 48 of 55

File: USPT

Apr 3, 1979

DOCUMENT-IDENTIFIER: US 4147869 A

TITLE: 3,4-Dihydrocarbostyryl derivatives and process for preparing the same

Brief Summary Paragraph Right (7):

Recently, carbostyryl compounds having a (2-hydroxy-3-substituted-amino)propoxy group at the 5-position of the carbostyryl or 3,4-dihydrocarbostyryl nucleus were found to have a cardioselective .beta.-adrenoreceptor blocking activity, as disclosed in German Patent Application No. DT 2,615,406 and U.S. application Ser. No. 778,539 filed on Mar. 17, 1977 (German Patent Application No. P27 11 719.7 filed on Mar. 17, 1977). Such cardioselective .beta.-blockers would be very useful for treatment of cardiac disorders such as angina pectoris, heart arrhythmia and hypertension. The compounds of the present invention were also found to have excellent cardioselectivity better than that of these known compounds and are useful in treatment or prophylaxis of cardiac disorders in subjects suffering also from chronic obstructive lung disease such as bronchial asthma.

49. Document ID: WO 9726327 A1

L14: Entry 49 of 55

File: EPAB

24, 1997

Jul

DOCUMENT-IDENTIFIER: WO 9726327 A1

TITLE: COMPOSITIONS AND METHODS FOR MEDIATING CELL CYCLE PROGRESSION

Abstract (1):

CHG DATE=19990617 STATUS=O>Hypercellular nonhuman organisms have functionally inactivated expression of a cyclin inhibitor gene, especially p27. The growth rate of nonhuman organisms are increased such that a desired size is attained more quickly than as compared to nonvariant organisms. Inhibitors of the p27 cyclin dependent kinase inhibitor protein or sequences encoding the protein modulate vertebrate cell cycle progression and increase the proportion of dividing cells to non-dividing cells in a population of treated cells. As the proportion of dividing cells increases, the cell population, e.g., hematopoietic progenitor (stem) cells, is more efficiently used for gene therapy applications. Transgenic animals and plants, and knockout alleles are provided.

50. Document ID: WO 200034308 A2, AU 200021728 A, EP 1137664 A2

L14: Entry 50 of 55

File: DWPI

Jun 15, 2000

DERWENT-ACC-NO: 2000-431269  
DERWENT-WEEK: 200037  
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TITLE: Protein transduction system for treating cancer and pathogenic infections has a fusion protein comprising a protein transduction domain covalently linked to a cytotoxic domain

Basic Abstract Text:

USE - (I) is useful for treating pathogen infection in mammals, infections such as CMV, HSV-1, HCV, KSHV, yellow fever virus, flavivirus or rhinovirus, retroviral infections such as HIV-1, HIV-2, HTLV-3 and/or LAV, plasmodial infections associated with P.faci-parum, P.vivax, P.ovale, P.malariae, cancer especially prostate cancer in which diseased cells express of property which can be targeted, such as elevated level of heavy metals e.g. zinc which promotes an inactive monomeric protein to become an active dimer. (I) is also useful for suppressing tumors by administering (I) comprising a cell cycle inhibitor such as p16, p27 or Cdk2DN along with a chemotherapeutic agent such as a DNA synthesis inhibitor that interacts in the S-phase of a targeted cell or a DNA damage initiator and thus promoting apoptosis (claimed).

Basic Abstract Text (17):

USE - (I) is useful for treating pathogen infection in mammals, infections such as CMV, HSV-1, HCV, KSHV, yellow fever virus, flavivirus or rhinovirus, retroviral infections such as HIV-1, HIV-2, HTLV-3 and/or LAV, plasmodial infections associated with P.faci-parum, P.vivax, P.ovale, P.malariae, cancer especially prostate cancer in which diseased cells express of property which can be targeted, such as elevated level of heavy metals e.g. zinc which promotes an inactive monomeric protein to become an active dimer. (I) is also useful for suppressing tumors by administering (I) comprising a cell cycle inhibitor such as p16, p27 or Cdk2DN along with a chemotherapeutic agent such as a DNA synthesis inhibitor that interacts in the S-phase of a targeted cell or a DNA damage initiator and thus promoting apoptosis (claimed).

51. Document ID: WO 200012679 A1, AU 9955869 A, EP 1108008 A1

L14: Entry 51 of 55

File: DWPI

Mar 9, 2000

DERWENT-ACC-NO: 2000-256635  
DERWENT-WEEK: 200022  
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Novel nucleic acid for screening compounds useful for treating proliferative and differentiative disorders such as cancer and immune disorders comprises sequences encoding ubiquitin ligases

Basic Abstract Text:

(12) a method for screening compounds to treat proliferative and differentiative disorders comprising contacting the compound with a cell or cell extract expressing Skp2, and one or more of p27 and E2F, and

detecting a change in Skp2 activity.

Basic Abstract Text (19):

(12) a method for screening compounds to treat proliferative and differentiative disorders comprising contacting the compound with a cell or cell extract expressing Skp2, and one or more of p27 and E2F, and detecting a change in Skp2 activity.

52. Document ID: WO 9937331 A1, AU 9925609 A, EP 1056478 A1

L14: Entry 52 of 55

File: DWPI

29, 1999

Jul

DERWENT-ACC-NO: 1999-458612  
DERWENT-WEEK: 199938  
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: New genetic construct, useful for gene therapy of cancers

Basic Abstract Text:

USE - (I) Within (II) may be administered to patients. This may be performed ex vivo by transfect an endothelial, hepatocyte, dendritic or monocyte cell population with (I) within (II). This group of cells is then be administered to a patient. Alternatively (I) within (II) may be administered directly to patients to target (I) to endothelial, hepatocyte, dendritic or monocyte cells within the body as part of a gene therapy regime. This protocol may be used to treat cancers where (I) codes for a cytostatic or cytotoxic protein such as p21 or p27. The method may also be used to treat cardiovascular or ischemic vascular disease where (I) encodes angiogenic factors such as VEGF or basic or acidic FGFs. Vasoplasm may also be treated this way if (I) encodes NO synthase or heme oxygenase. In addition monocytes and dendritic cells may be targeted with genes encoding immunogens for cell-targeted immunization.

Basic Abstract Text (4):

USE - (I) Within (II) may be administered to patients. This may be performed ex vivo by transfect an endothelial, hepatocyte, dendritic or monocyte cell population with (I) within (II). This group of cells is then be administered to a patient. Alternatively (I) within (II) may be administered directly to patients to target (I) to endothelial, hepatocyte, dendritic or monocyte cells within the body as part of a gene therapy regime. This protocol may be used to treat cancers where (I) codes for a cytostatic or cytotoxic protein such as p21 or p27. The method may also be used to treat cardiovascular or ischemic vascular disease where (I) encodes angiogenic factors such as VEGF or basic or acidic FGFs. Vasoplasm may also be treated this way if (I) encodes NO synthase or heme oxygenase. In addition monocytes and dendritic cells may be targeted with genes encoding immunogens for cell-targeted immunization.

53. Document ID: JP 2001510028 W, WO 9903508 A2, AU 9885021 A, EP 998307 A2, US 6177272 B1

L14: Entry 53 of 55

File: DWPI

1/1

31, 2001

DERWENT-ACC-NO: 1999-131876  
DERWENT-WEEK: 200148  
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TITLE: Treating vascular proliferative disease with p27 gene - used particularly to treat restenosis, atherosclerosis and angiogenesis or to inhibit intimal smooth muscle cell growth

Basic Abstract Text:

USE - (I) is used to treat, or prevent, restenosis (coronary or peripheral), atherosclerosis or angiogenesis, or generally to inhibit growth of intimal smooth muscle cells. The method is based on the discovery that p27 functions in arteries to control response to acute injury and cell proliferation. Its (over)expression is sufficient to inhibit growth of vascular smooth muscle cells in vivo.

Equivalent Abstract Text:

USE - (I) is used to treat, or prevent, restenosis (coronary or peripheral), atherosclerosis or angiogenesis, or generally to inhibit growth of intimal smooth muscle cells. The method is based on the discovery that p27 functions in arteries to control response to acute injury and cell proliferation. Its (over)expression is sufficient to inhibit growth of vascular smooth muscle cells in vivo.

Basic Abstract Text (2):

USE - (I) is used to treat, or prevent, restenosis (coronary or peripheral), atherosclerosis or angiogenesis, or generally to inhibit growth of intimal smooth muscle cells. The method is based on the discovery that p27 functions in arteries to control response to acute injury and cell proliferation. Its (over)expression is sufficient to inhibit growth of vascular smooth muscle cells in vivo.

Equivalent Abstract Text (2):

USE - (I) is used to treat, or prevent, restenosis (coronary or peripheral), atherosclerosis or angiogenesis, or generally to inhibit growth of intimal smooth muscle cells. The method is based on the discovery that p27 functions in arteries to control response to acute injury and cell proliferation. Its (over)expression is sufficient to inhibit growth of vascular smooth muscle cells in vivo.

54. Document ID: EP 1023005 A1, WO 9900071 A1, AU 9882676 A

L14: Entry 54 of 55

File: DWPI

Aug 2, 2000

DERWENT-ACC-NO: 1999-105646  
DERWENT-WEEK: 200038  
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TITLE: New device comprising an intravascular stent coated with a polymerizable matrix - useful for expressing therapeutically useful amounts of recombinant genes in vivo and for treating vascular diseases, especially restenosis

Basic Abstract Text:

USE - The device is useful for expressing therapeutically useful amounts of recombinant genes in vivo (useful proteins include antiplatelet, anticoagulant, antimitotic, antioxidant, antimetabolite or

antiinflammatory agents, which inhibit cell proliferation, and retinoblastoma, p16, p21, p27, p57, especially thymidine kinase or cytosine deaminase), and for treating vascular diseases (particularly restenosis, atherosclerosis, coronary artery bypass graft stenosis/restenosis, arterio-venous fistula stenosis/restenosis, or peripheral artery stenosis/restenosis), where the device is placed into the vasculature of a patient (claimed).

Basic Abstract Text (2):

USE - The device is useful for expressing therapeutically useful amounts of recombinant genes in vivo (useful proteins include antiplatelet, anticoagulant, antimitotic, antioxidant, antimetabolite or antiinflammatory agents, which inhibit cell proliferation, and retinoblastoma, p16, p21, p27, p57, especially thymidine kinase or cytosine deaminase), and for treating vascular diseases (particularly restenosis, atherosclerosis, coronary artery bypass graft stenosis/restenosis, arterio-venous fistula stenosis/restenosis, or peripheral artery stenosis/restenosis), where the device is placed into the vasculature of a patient (claimed).

55. Document ID: JP 2000503538 W, WO 9726327 A1, AU 9717507 A, EP 877796 A1, AU 705640 B, US 5958769 A

L14: Entry 55 of 55

File: DWPI

Mar 28, 2000

DERWENT-ACC-NO: 1997-385332  
DERWENT-WEEK: 200026  
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TITLE: Hypertrophic variant organism with inactivated cyclin inhibitor gene - useful as models for therapy of abnormal cell proliferation diseases, e.g. hyperplasia

Basic Abstract Text:

USE - The p27 inhibitor can be used in a method for increasing the efficiency of transducing a vertebrate cell population with a viral vector encoding a gene product of interest (claimed). The growth rate of a non-human organism can be increased by functionally inactivating the expression of a cyclin inhibitor gene (claimed). The non-human organisms of (2) can be used as models for studying disease pathogenesis, and fundamental cell biology, as well as providing useful models for screening for novel therapeutic agents to treat diseases related to abnormal cell proliferation, e.g. neoplasia, hyperplasia, inflammation, AIDS and Alzheimer's disease.

Equivalent Abstract Text:

USE - The p27 inhibitor can be used in a method for increasing the efficiency of transducing a vertebrate cell population with a viral vector encoding a gene product of interest (claimed). The growth rate of a non-human organism can be increased by functionally inactivating the expression of a cyclin inhibitor gene (claimed). The non-human organisms of (2) can be used as models for studying disease pathogenesis, and fundamental cell biology, as well as providing useful models for screening for novel therapeutic agents to treat diseases related to abnormal cell proliferation, e.g. neoplasia, hyperplasia, inflammation, AIDS and Alzheimer's disease.

Basic Abstract Text (2):

USE - The p27 inhibitor can be used in a method for increasing the efficiency of transducing a vertebrate cell population with a viral vector encoding a gene product of interest (claimed). The growth rate of a non-human organism can be increased by

functionally inactivating the expression of a cyclin inhibitor gene (claimed).  
The non-human organisms of (2) can be used as models for studying disease pathogenesis, and fundamental cell biology, as well as providing useful models for screening for novel therapeutic agents to treat diseases related to abnormal cell proliferation, e.g. neoplasia, hyperplasia, inflammation, AIDS and Alzheimer's disease.

Equivalent Abstract Text (2):

USE - The p27 inhibitor can be used in a method for increasing the efficiency of transducing a vertebrate cell population with a viral vector encoding a gene product of interest (claimed). The growth rate of a non-human organism can be increased by functionally inactivating the expression of a cyclin inhibitor gene (claimed).  
The non-human organisms of (2) can be used as models for studying disease pathogenesis, and fundamental cell biology, as well as providing useful models for screening for novel therapeutic agents to treat diseases related to abnormal cell proliferation, e.g. neoplasia, hyperplasia, inflammation, AIDS and Alzheimer's disease.

09/208276  
JH/14

=> s p27 or kip1  
L1 11535 P27 OR KIP1

=> s catheter  
L2 188186 CATHETER

=> s l1 and l2  
L3 12 L1 AND L2

=> dup rem l3  
PROCESSING COMPLETED FOR L3  
L4 8 DUP REM L3 (4 DUPLICATES REMOVED)

=> d l4 ibib abs 1-8

L4 ANSWER 1 OF 8 EMBASE COPYRIGHT 2003 ELSEVIER SCI.  
B.V.

ACCESSION NUMBER: 2003087649 EMBASE

TITLE: Retinoids: Pleiotropic agents of therapy for vascular diseases?

AUTHOR: Streb J.W.; Miano J.M.

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026 Immunology, Serology and Transplantation

030 Pharmacology

037 Drug Literature Index

038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Retinoids, the natural and synthetic derivatives of vitamin A, exert broad biological effects and have been used clinically to treat a variety of dermatological and neoplastic diseases. The principal mode of action of many retinoids is through the binding and activation of a family of nuclear receptors that modulate gene transcription. Recent evidence demonstrates that retinoids effectively attenuate experimental vessel wall narrowing due to atherosclerosis, post-balloon injury stenosis, and bypass graft failure. Moreover, retinoids promote a differentiated phenotype in smooth muscle cells (SMC) which, unlike other muscle types, is not fixed and is subject to considerable modulation in disease states. A growing number of in vitro studies have reported desirable effects of retinoids on cell migration, proliferation, apoptosis, matrix remodeling, fibrinolysis, coagulation, and inflammation, all of which impinge on vascular disease. Since vascular SMC and endothelial cells (EC) express most retinoid receptors, the mechanisms underlying retinoid-mediated events in these cells and the vessel wall likely relate to an altered transcriptome. In fact, there is a growing list of retinoid-response genes encoding proteins that likely mediate the actions of retinoids. Retinoid-response genes, therefore, represent promising targets of therapy for the refined treatment of vascular diseases. The purpose of this review is to summarize the emerging importance of retinoids in the control of vascular cell responses with special emphasis on potential mechanisms underlying retinoid-induced changes in the vessel wall following injury. Given the similarities in the pathogenesis of neoplasia and vascular disease, it is reasonable to consider testing the efficacy of retinoids for the treatment of human vascular disease.

L4 ANSWER 2 OF 8 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2002-590578 [63] WPIDS

DOC. NO. NON-CPI: N2002-468664

DOC. NO. CPI: C2002-167041

TITLE: Dispensing a therapeutic agent in situ to a localized region e.g. a tumor useful for gene therapy comprises administering a polymer composition, a cross-linking composition and the therapeutic agent to the region.

DERWENT CLASS: A96 B04 B05 D16 P31

INVENTOR(S): AZHDARINIA, A; KIM, E E; LEE, T L; YANG, D J;

YU, D

PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM

COUNTRY COUNT: 98

PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG

WO 2002049501 A2 20020627 (200263)\* EN 116

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE  
LS LU MC MW MZ

NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN  
CO CR CU CZ DE DK

DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP  
KE KG KP KR

KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ  
NO NZ OM PH PL PT

RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU  
ZA ZM ZW

AU 2002031041 A 20020701 (200264)

APPLICATION DETAILS:

PATENT NO KIND APPLICATION DATE

WO 2002049501 A2

WO 2001-US49087 20011218

AU 2002031041 A

AU 2002-31041 20011218

FILING DETAILS:

PATENT NO KIND

PATENT NO

AU 2002031041 A Based on

WO 200249501

PRIORITY APPLN. INFO: US 2000-256514P 20001218

AN 2002-590578 [63] WPIDS

AB WO 200249501 A UPAB: 20021031

NOVELTY - Dispensing (M1) a therapeutic agent in situ to a localized region in an individual comprising administering a biocompatible polymer composition (a), a cross-linking composition (b) and the therapeutic agent to the region to allow formation of a cross-linked polymer in situ at the region, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) treating a tumor in situ, occluding an artery associated with a tumor in an individual or providing a slow-release hydrogel composition in situ to a tumor involving administering to the tumor (a), (b) and the therapeutic agent; and

(2) a kit for treating a tumor in situ and for occluding an artery associated with a tumor in an individual comprising, a first container with (a) and a second container with (b) in a container.

ACTIVITY - Cytostatic; Antitumor.

Rats with mammary tumor were used in the study. Cisplatin was suspended in sodium alginate to prepare SA-CDDP (5.4 mg cisplatin/ml).

The

SA-CDDP (0.1 ml, cisplatin dose was 3 mg/kg body weight) was injected directly into the tumors. Calcium chloride (8% in water) was then injected into the same place to form cisplatin-loaded alginate beads in the tumors. The tumor size was measured to determine the anticancer effect and blood chemical assay (blood urea nitrogen (BUN) and serum creatinine) were performed to detect renal toxicity. After injection, tumor volume decreased as a function of time. No tumor relapse had occurred in the rats 5 months after treatment. BUN and serum creatinine levels after intratumoral injection of SA-CDDP was in the normal range. On day 40,

BUN

in five experimental rats and five healthy rats (control) were 18.30 plus or minus 1.51 mg/dl and 17.88 plus or minus 2.24 mg/dl respectively.

Serum

creatinine levels were the same as in both experimental and control rats (0.6 mg/dl). In rats treated with CDDP intratumorally, a clear nephrotoxicity was observed as evidenced by increased BUN and creatinine levels.

MECHANISM OF ACTION - None given.

USE - (M1) is used for dispensing a therapeutic agent in situ to a localized region in an individual, for treating a tumor in situ, for occluding an artery associated with a tumor and for providing a slow-release hydrogel composition in situ to a tumor.

SE SG SI SK SL TJ  
TM TR TT UA UG US UZ VN YU ZA ZW  
AU 9955725 A 20000314 (200031)  
EP 1104463 A1 20010606 (200133) EN  
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT  
SE

APPLICATION DETAILS:

| PATENT NO     | KIND | APPLICATION     | DATE     |
|---------------|------|-----------------|----------|
| WO 2000011165 | A1   | WO 1999-US18903 | 19990820 |
| AU 9955725    | A    | AU 1999-55725   | 19990820 |
| EP 1104463    | A1   | EP 1999-942320  | 19990820 |
|               |      | WO 1999-US18903 | 19990820 |

FILING DETAILS:

| PATENT NO  | KIND        | PATENT NO    |
|------------|-------------|--------------|
| AU 9955725 | A Based on  | WO 200011165 |
| EP 1104463 | A1 Based on | WO 200011165 |

PRIORITY APPLN. INFO: US 1998-97710P 19980821

AN 2000-237648 [20] WPIDS

AB WO 200011165 A UPAB: 20000426

NOVELTY - A novel DNA sequence (I) encoding human KIS (hKIS) which acts as

an inhibitory kinase of the cyclin-dependent kinase inhibitor (CKI) \*\*\*p27\*\*\*, and allows the modulation of cell proliferation, is new.

DETAILED DESCRIPTION - (I) comprises at least 63 contiguous nucleotides of the 1260 bp sequence given in the specification or the complement thereof.

INDEPENDENT CLAIMS are also included for the following:

- (1) an isolated nucleic acid (NA) (I) encoding a transdominant negative hKIS protein;
- (2) an isolated NA (II) encoding a CKI containing a mutation at a serine or threonine, wherein the CKI retains its ability to arrest cells in G1 phase;
- (3) a polypeptide, encoded within an expression vector, comprising the CKI of (2);
- (4) inhibiting cell proliferation comprising contacting the cells with a NA encoding a CKI protein that is not functionally inhibited by a serine/threonine kinase;
- (5) kits comprising the isolated NA in (1) and (2);
- (6) inhibiting the proliferation of a cell, comprising contacting the cell with a composition inhibiting phosphorylation of \*\*\*p27\*\*\* by hKIS;
- (7) treating a patient, comprising administering an isolated NA encoding a CKI protein that is not functionally inhibited by a serine/threonine kinase;
- (8) treating or otherwise ameliorating a cell proliferative disorder in a patient, comprising providing to a proliferating cell a cyclin-dependent kinase modified at a serine or threonine residue such that the kinase is not phosphorylated by a serine/threonine kinase; and
- (9) a kit comprising a \*\*\*catheter\*\*\* and a solution comprising a NA encoding a cyclin kinase inhibitor with a mutation at a Ser or The codon, which retains its ability to arrest cells in G1 phase.

ACTIVITY - Serine/threonine kinase.

MECHANISM OF ACTION - hKIS binds to the cyclin-dependent kinase inhibitor (CKI) \*\*\*p27\*\*\*, and inhibits its ability to arrest cells in G1 phase.

USE - The hKIS polynucleotides and polypeptides are used to modulate cell proliferation, and to treat cell proliferative diseases and vascular diseases. The hKIS polynucleotide may be used in gene therapy.

ADVANTAGE - None given.

Dwg.0/1

L4 ANSWER 7 OF 8 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 2

ACCESSION NUMBER: 2000141780 EMBASE  
TITLE: Proliferation of intimal smooth muscle cells. Attenuation of basic fibroblast growth factor 2-stimulated proliferation is associated with increased expression of cell cycle inhibitors.

AUTHOR: Olson N.E.; Kozlowski J.; Reidy M.A.

CORPORATE SOURCE: N.E. Olson, Dept. of Pathology, Box 357335, University of

Washington, Seattle, WA 98195, United States.

olsonne@u.washington.edu

SOURCE: Journal of Biological Chemistry, (14 Apr 2000) 275/15 (11270-11277).

Refs: 60

ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Basic fibroblast growth factor (FGF2) is a potent mitogen for medial smooth muscle cells and is necessary for their proliferation after balloon \*\*\*catheter\*\*\* injury; however, intimal smooth muscle cells do not require FGF2 for their proliferation, and they respond only weakly to exogenous FGF2. The present study examined the activation of extracellular

signal-regulated kinase (ERK) signaling as well as the expression and activity of cell cycle proteins in FGF2-stimulated intimal smooth muscle cells. FGF2 activates ERKs 1 and 2, and Western blot analysis showed that

cyclin D, cyclin E, and cyclin-dependent kinase (CDKs) 2 and 4 were expressed in intimal smooth muscle cells after FGF2 infusion. FGF2 stimulation, however, did not lead to phosphorylation of the retinoblastoma protein (Rb), CDK 2 activation, or expression of cyclin A. Western blot analysis showed that intimal smooth muscle cells express elevated levels of the cell cycle inhibitors p15(INK4b) and \*\*\*p27\*\*\* (\*\*\*Kip1\*\*\*), compared with medial smooth muscle cells, and that

FGF2 stimulation does not reduce the level of these inhibitors. These studies suggest that despite activation of ERKs 1 and 2 and expression of the cell cycle activators, cyclin D and cyclin E, high levels of cell cycle inhibitors may inhibit cell cycle transit in FGF2-stimulated intimal smooth muscle cells.

L4 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:184581 BIOSIS

DOCUMENT NUMBER: PREV199799483784

TITLE: Loss of \*\*\*p27\*\*\* - \*\*\*Kip1\*\*\* and induction of Cdk1 in the rat carotid artery following balloon \*\*\*catheter\*\*\* injury. In vivo and in vitro influence of rapamycin.

AUTHOR(S): Braun-Dullaeus, R. C. (1); Von Der Leyen, H. E.; Mann, M.

J. (1); Zhang, L. (1); Morris, R. E.; Dzau, V. J. (1)

CORPORATE SOURCE: (1) Dep. Med., Brigham and Women's Hosp., Boston, MA USA

SOURCE: FASEB Journal, (1997) Vol. 11, No. 3, pp. A153.

Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 97 New Orleans, Louisiana, USA April 6-9, 1997

ISSN: 0892-6638.

DOCUMENT TYPE: Conference; Abstract

LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 15:55:01 ON 26 APR 2003)

FILE 'BIOSIS, EMBASE, MEDLINE, WPIDS, HCAPLUS' ENTERED AT 15:55:10 ON 26

APR 2003

L1 11535 S P27 OR KIP1

L2 188186 S CATHETER

L3 12 S L1 AND L2

L4 8 DUP REM L3 (4 DUPLICATES REMOVED)

=> s express?

L5 3350804 EXPRESS?

=> s treat? or pharma?

2 FILES SEARCHED...

L6 12514314 TREAT? OR PHARMA?

=> s l1 and l5

L7 7407 L1 AND L5

=> s l1 and l6

L8 3563 L1 AND L6

=> s artery or vein or vascular?

COMMAND INTERRUPTED

If this message appears repeatedly, please notify the Help Desk.

Enter "HELP STN" for information on contacting the nearest STN Help Desk by telephone or via SEND in the STNMAIL file.

=> s l7 or l8

L9 8448 L7 OR L8

=> s l9 and (artery or vein or vascular or vasculature)

L10 502 L9 AND (ARTERY OR VEIN OR VASCULAR OR VASCULATURE)

=> dup rem l10

PROCESSING COMPLETED FOR L10

L11 272 DUP REM L10 (230 DUPLICATES REMOVED)

=> s l11 and py<1998

2 FILES SEARCHED...

4 FILES SEARCHED...

L12 15 L11 AND PY<1998

=> d l12 ibib abs 1-15

L12 ANSWER 1 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1998:15426 BIOSIS

DOCUMENT NUMBER: PREV199800015426

TITLE: Differential \*\*\*expression\*\*\* of p27Kip1, p21Cip1 and P16INK cyclin-dependent kinase inhibitors in \*\*\*vascular\*\*\* disease.

AUTHOR(S): Tanner, Felix C.; Yang, Zhi-Yong; Gordon, David; Nabel, Gary J.; Nabel, Elizabeth G.

CORPORATE SOURCE: Univ. Michigan, Ann Arbor, MI USA

SOURCE: Circulation, ( \*\*\*10/21/97, 1997\*\*\* ) Vol. 96, No. 8 SUPPL., pp. I46.

Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997 ISSN: 0009-7322.

DOCUMENT TYPE: Conference

LANGUAGE: English

L12 ANSWER 2 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:522664 BIOSIS

DOCUMENT NUMBER: PREV199799821867

TITLE: The role of proto-oncogenes in coronary restenosis.

AUTHOR(S): Muller, David W. M.

CORPORATE SOURCE: Dep. Cardiol., St. Vincent's Hosp., Victoria St., Darlinghurst, NSW 2010 Australia

SOURCE: Progress in Cardiovascular Diseases, (1997) Vol. 40, No. 2,

pp. 117-128.

ISSN: 0033-0620.

DOCUMENT TYPE: General Review

LANGUAGE: English

L12 ANSWER 3 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:292272 BIOSIS

DOCUMENT NUMBER: PREV199799591475

TITLE: Protein kinase C delta inhibits the proliferation of \*\*\*vascular\*\*\* smooth muscle cells by suppressing G-1 cyclin \*\*\*expression\*\*\*.

AUTHOR(S): Fukumoto, Shinya (1); Nishizawa, Yoshiki; Hosoi, Masayuki;

Koyama, Hidenori; Yamakawa, Kenjiro; Ohno, Shigeo; Morii, Hirotoishi

CORPORATE SOURCE: (1) Second Dep. Intern. Med., Osaka City Univ. Med. Sch.,

Osaka 545 Japan

SOURCE: Journal of Biological Chemistry, (1997) Vol. 272, No. 21, pp. 13816-13822.

ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

AB To elucidate the physiological role of protein kinase C (PKC) delta, a ubiquitously \*\*\*expressed\*\*\* isoform in \*\*\*vascular\*\*\* smooth muscle cells (VSMC), PKC delta was stably overexpressed in A7r5 cells, rat clonal VSMC. The (3H)thymidine incorporation in A7r5 overexpressed with

PKC delta (DVs) was suppressed to 37.1 +/- 16.3% (mean +/- S.D.) of the level in control or A7r5 transfected with vector alone (EVs). The reduction of (3H)thymidine incorporation was strongly correlated with overexpressed PKC levels. Moreover, transient transfection of a dominant negative mutant of PKC delta restored the reduced proliferation in DVs. Flow cytometry analysis demonstrated that DVs were arrested in the G-0/G-1

phase of the cell cycle. \*\*\*Expression\*\*\* of cyclins D1 and E and retinoblastoma protein phosphorylation were reduced, while the protein levels of \*\*\*p27\*\*\* were elevated in DVs as compared with EVs.

There

were no significant differences in the \*\*\*expression\*\*\* of c-fos, c-jun, c-myc, cyclin D2, D3, cyclin-dependent kinase 2, cyclin-dependent kinase 4, and p21 among the clones. We conclude that PKC delta inhibits the proliferation of VSMC by arresting cells in G-1 via mainly inhibiting the \*\*\*expression\*\*\* of cyclin D1 and cyclin E.

L12 ANSWER 4 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:291867 BIOSIS

DOCUMENT NUMBER: PREV199799591070

TITLE: Downregulation of cyclin-dependent kinase 2 activity and cyclin A promoter activity in \*\*\*vascular\*\*\* smooth muscle cells by \*\*\*p27\*\*\* - \*\*\*KIP1\*\*\*, an inhibitor of neointima formation in the rat carotid \*\*\*artery\*\*\*.

AUTHOR(S): Chen, Donghui; Krasinski, Kevin; Chen, Dongfen; Sylvester, Amy; Chen, Jun; Nisen, Perry D.; Andres, Vicente (1)

CORPORATE SOURCE: (1) Div. Cardiovascular Research, St. Elizabeth's Med. Center, 736 Cambridge St., Boston, MA 02135 USA

SOURCE: Journal of Clinical Investigation, (1997) Vol. 99, No. 10, pp. 2334-2341.

ISSN: 0021-9738.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Abnormal proliferation of \*\*\*vascular\*\*\* smooth muscle cells (VSMCs)

contributes to intimal hyperplasia during atherosclerosis and restenosis, but the endogenous cell cycle regulatory factors underlying VSMC growth in

response to arterial injury are not well understood. In the present study, we report that downregulation of cyclin-dependent kinase 2 (cdk2) activity in serum-deprived VSMCs was associated with the formation of complexes

between cdk2 and its inhibitory protein \*\*\*p27\*\*\* - \*\*\*KIP1\*\*\* ( \*\*\*p27\*\*\* ). Ectopic overexpression of \*\*\*p27\*\*\* in

serum-stimulated VSMCs resulted in the inhibition of cdk2 activity and repression of cyclin A promoter activity. Collectively, these findings indicate that \*\*\*p27\*\*\* may contribute to VSMC growth arrest in vitro. Using the rat

carotid model of balloon angioplasty, a marked upregulation of \*\*\*p27\*\*\*

was observed in injured arteries. High levels of \*\*\*p27\*\*\* \*\*\*expression\*\*\* in the media and neointima correlated with downregulation of cdk2 activity at 2 wk after angioplasty, and adenovirus-mediated overexpression of \*\*\*p27\*\*\* in balloon-injured arteries attenuated neointimal lesion formation. Thus, the inhibition of cdk2 function and repression of cyclin A gene transcription through the induction of the endogenous \*\*\*p27\*\*\* protein provides a mechanism for

the inhibition of VSMC growth at late time points after angioplasty.

09/708276  
74#6

=> s p27 or kip or kip1  
L1 10177 P27 OR KIP OR KIP1

=> s catheter?  
L2 316432 CATHETER?

=> s l1 and l2  
L3 10 L1 AND L2

=> dup rem l3  
PROCESSING COMPLETED FOR L3  
L4 6 DUP REM L3 (4 DUPLICATES REMOVED)

=> d l4 ibib abs l-6

L4 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL  
ABSTRACTS INC.DUPLICATE 1

ACCESSION NUMBER: 2001:460576 BIOSIS  
DOCUMENT NUMBER: PREV200100460576

TITLE: \*\*\*p27\*\*\* -p16 fusion gene inhibits angioplasty-induced  
neointimal hyperplasia and coronary artery occlusion.

AUTHOR(S): Tsui, Lisa V.; Camrud, Allan; Mondesire, Jean; Carlson,  
Paula; Zayek, Nathalie; Camrud, LaDonna; Donahue, Brian;  
Bauer, Scott; Lin, Andy; Frey, David; Rivkin, Marianne;  
Subramanian, Ajit; Falotico, Robert; Gyuris, Jeno;  
Schwartz, Robert; McArthur, James G. (1)

CORPORATE SOURCE: (1) Department of Preclinical Biology and  
Immunology, Cell

Genesys Inc, 342 Lakeside Dr, Foster City, CA, 94404:  
jamesm@cellgenesys.com USA

SOURCE: Circulation Research, (August 17, 2001) Vol. 89, No. 4,  
pp.

323-328, print.  
ISSN: 0009-7330.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Inhibition of proliferative neointima formed by vascular smooth muscle  
cells is a potential target in preventing angioplasty-induced restenosis.

We have created a potent antiproliferative by fusing the active regions of  
the \*\*\*p27\*\*\* and p16 cell cycle inhibitors. Intravascular delivery of  
a replication-deficient adenoviral vector (AV) encoding this \*\*\*p27\*\*\*  
-p16 fusion protein, named W9, inhibited balloon injury-induced  
neointimal

hyperplasia in rabbit carotid arteries. In a therapeutically more relevant  
model, AV-W9 was delivered to balloon-injured porcine coronary arteries  
in

vivo using an infusion \*\*\*catheter\*\*\*. Of the three coronary arteries,  
two were injured with a 1.5-mm balloon \*\*\*catheter\*\*\* and either were  
left untreated or were treated with 1012 viral particles of either AV-W9  
or a control null virus. AV-W9 treatment significantly inhibited  
neointimal hyperplasia in this porcine arterial balloon injury model  
compared with untreated or control virus-treated vessels. The average  
intimal area of the AV-W9-treated group 10 days after balloon injury and  
treatment was 0.42+0.36 mm<sup>2</sup>, whereas the AV-null group demonstrated

an  
intimal area of 0.70+0.52 mm<sup>2</sup>. At day 10 the average intimal thickness  
of

the AV-W9-treated vessels was 9.1 mum (n=5, X20 magnification)

compared  
with 21.2 mum (n=5, X20 magnification) in control virus-treated vessels.  
This trend was also observed at 28 days after balloon injury and gene  
transfer during which AV-W9-treated vessels demonstrated an average  
intimal thickness of 4.7 mum (n=8, X20 magnification) compared with

13.3  
mum (n=3, X20 magnification) in control virus-treated vessels and 7.3  
mum

(n=5, X20 magnification) in the sham-treated vessels. The AV-W9  
treatment

was safe and well tolerated. These data suggest that AV-W9 gene therapy  
may be useful in preventing angioplasty-induced intimal hyperplasia in the  
coronary artery.

L4 ANSWER 2 OF 6 WPIDS COPYRIGHT 2002 DERWENT  
INFORMATION LTD

ACCESSION NUMBER: 2000-452281 [39] WPIDS

DOC. NO. CPL: C2000-137857

TITLE: Treating a cardiovascular condition comprises infusing a  
recombinant adeno-associated virus vector encoding a  
therapeutically-effective molecule into a coronary artery  
or sinus to transduce cardiomyocytes.

DERWENT CLASS: B04 C06 D16

INVENTOR(S): LEIDEN, J M; SVENSSON, E

PATENT ASSIGNEE(S): (ARCH-N) ARCH DEV CORP

COUNTRY COUNT: 90

PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG

WO 2000038518 A1 20000706 (200039)\* EN 20

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE  
LS LU MC MW NL

OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU  
CZ DE DK DM EE ES

FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ  
LC LK LR LS

LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU  
SD SE SG SI SK SL

TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000023942 A 20000731 (200050)

EP 1139751 A1 20011010 (200167) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV  
MC MK NL PT

RO SE SI

APPLICATION DETAILS:

PATENT NO KIND APPLICATION DATE

WO 2000038518 A1 WO 1999-US31093 19991228

AU 2000023942 A AU 2000-23942 19991228

EP 1139751 A1 EP 1999-967703 19991228

WO 1999-US31093 19991228

FILING DETAILS:

PATENT NO KIND PATENT NO

AU 2000023942 A Based on WO 200038518

EP 1139751 A1 Based on WO 200038518

PRIORITY APPLN. INFO: US 1998-113923P 19981228

AN 2000-452281 [39] WPIDS

AB WO 200038518 A UPAB: 20000818

NOVELTY - Treating a cardiovascular condition comprises infusing a  
recombinant adeno-associated virus (AAV) vector encoding a nucleic acid  
for a therapeutically-effective molecule operably linked to a control  
region into a coronary artery or sinus to transduce cardiomyocytes.

ACTIVITY - Vasotropic; antiarteriosclerotic; antiarrhythmic. No  
biological data is given.

MECHANISM OF ACTION - Cardiomyocyte transducer. Hearts  
from C57BL/6

mice were explanted and perfused with 1.5 x 10<sup>9</sup> infectious units of  
AVVCMV-LacZ for 15 minutes at 4 deg. C via a \*\*\*catheter\*\*\* placed

in  
the left common carotid artery. The perfused hearts were then  
transplanted into syngeneic hosts, and arterial circulation was  
reestablished by anastomosis of the transplanted aorta to the recipient  
carotid artery. The transplanted and revascularized hearts resumed  
beating and continued to do so until the recipient mice were killed 2, 4,  
or 8 weeks after perfusion. About 40 % of cardiomyocytes were beta -gal  
positive 4 weeks after perfusion and greater than 50 % of the  
cardiomyocytes continued to express beta -gal weeks later.

USE - For treating a cardiovascular condition. For inducing or  
inhibiting angiogenesis or stimulating or inhibiting cell proliferation.  
For treating restenosis, atherosclerosis, congestive heart failure,  
ischemic cardiomyopathy or malignant arrhythmia (all claimed). Any

animal  
may be treated, for example, rodents, dogs, cats, cattle, primates, and  
humans. Human acquired or inherited cardiac conditions or diseases can

be  
treated through gene therapy.

ADVANTAGE - Stable and efficient gene transfer into the heart is  
achieved. No viral gene products are expressed so AAV vectors are 1

FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|---|------|----------|-----------------|----------|
| WO 9858989  | A1   | 19981230 | WO 1998-DK264   | 19980619 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |      |          |                 |          |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG  |      |          |                 |          |
| AU 9880117  | A1   | 19990104 | AU 1998-80117   | 19980619 |
| EP 991702   | A1   | 20000412 | EP 1998-928177  | 19980619 |
| EP 991702   | B1   | 20010822 |                 |          |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI   |      |          |                 |          |
| AT 204594   | E    | 20010915 | AT 1998-928177  | 19980619 |
| ES 2162453  | T3   | 20011216 | ES 1998-928177  | 19980619 |
| JP 2002505697   | T2   | 20020219 | JP 1999-503611  | 19980619 |

PRIORITY APPLN. INFO.: DK 1997-730 A 19970620  
WO 1998-DK264 W 19980619

AB Coating compn., useful medical devices such as \*\*\*catheters\*\*\*, comprises a crosslinkable hydrophilic polymer contg. ethylenically unsatd. group site-chain, and a water-sol. compd. Thus, a PVC \*\*\*catheter\*\*\* was dipped in a primer contg. Pladone K 90 (polyvinylpyrrolidone) 4.9, Esacure \*\*\*KIP\*\*\* 150 (UV catalyst) 0.1 and ethanol/gamma-butyrolactone (85/15) 95 parts, dried for 1 min at 60.degree., coated with a topcoat contg. PVP K 90 3.36, urea 0.64 and ethanol/gamma-butyrolactone (85/15) 95 parts, dried for 30 min at 60.degree. and exposed to UV-light, showing friction force 0.03 N initially, and 0.04 N after dipped in water for 8 min.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES  
AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L4 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL  
ABSTRACTS INC.  
ACCESSION NUMBER: 1997:184581 BIOSIS  
DOCUMENT NUMBER: PREV199799483784  
TITLE: Loss of \*\*\*p27\*\*\* - \*\*\*Kip1\*\*\* and induction of Cdk1  
in the rat carotid artery following balloon  
\*\*\*catheter\*\*\* injury. In vivo and in vitro influence of  
rapamycin.  
AUTHOR(S): Braun-Dullaeus, R. C. (1); Von Der Leyen, H. E.; Mann, M.  
J. (1); Zhang, L. (1); Morris, R. E.; Dzau, V. J. (1)  
CORPORATE SOURCE: (1) Dep. Med., Brigham and Women's Hosp.,  
Boston, MA USA  
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=> s angioplast? or cardiac or cardiovascular or heart or artery or arteries  
L5 3388096 ANGIOPLAST? OR CARDIAC OR CARDIOVASCULAR  
OR HEART OR ARTERY OR  
ARTERIES

=> s 11 and 15

L6 342 L1 AND L5

=> s expression or express or expressed or expressing

L7 2882904 EXPRESSION OR EXPRESS OR EXPRESSED OR  
EXPRESSING

=> s 11 and 15 and 17

L8 243 L1 AND L5 AND L7

=> s cytotoxic  
L9 272685 CYTOTOXIC

=> s tk or (thymidine kinase) or cd or (cytosine deaminase) or nos or (nitric  
oxide (synthase or synthetase))  
MISSING OPERATOR 'OXIDE (SYNTHASE'  
The search profile that was entered contains terms or  
nested terms that are not separated by a logical operator.

=> s tk or (thymidine kinase) or cd or (cytosine deaminase) or nos or ((nitric  
oxide(w)(synthase or synthetase))  
L10 637735 TK OR (THYMIDINE KINASE) OR CD OR (CYTOSINE  
DEAMINASE) OR NOS  
OR ((NITRIC OXIDE)(W)(SYNTHASE OR SYNTHETASE))

=> s fusion or chimera or chimeric  
L11 533969 FUSION OR CHIMERA OR CHIMERIC

=> s 11(1)17  
L12 5225 L1(L) L7

=> s 112 and 15  
L13 215 L12 AND L5

=> dup rem 113  
PROCESSING COMPLETED FOR L13  
L14 111 DUP REM L13 (104 DUPLICATES REMOVED)

=> s 114 and py<1998  
1 FILES SEARCHED...  
3 FILES SEARCHED...  
4 FILES SEARCHED...  
L15 22 L14 AND PY<1998

=> s 19 or 110

L16 902481 L9 OR L10

=> s 11 and 111 and 116

L17 28 L1 AND L11 AND L16

=> dup rem 117  
PROCESSING COMPLETED FOR L17  
L18 19 DUP REM L17 (9 DUPLICATES REMOVED)

=> s 115 or 118  
L19 41 L15 OR L18

=> d 119 ibib abs

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AUTHOR(S): Danthinne, Xavier; Aoki, Kazunori; Kurachi, Akiko L.;  
Nabel, Gary J.; Nabel, Elizabeth G. (1)  
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1150 W. Medical Center Dr., 7220 MSRB III, Ann Arbor, MI  
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